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Toxicity of drugs in the neonatal period

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CLINICAL experience has recently provided dramatic evidence that infants may respond abnormally to doses of drugs which are well tolerated by older children and adults. This testimony to developmental immaturity has in many instances become apparent through severe, often fatal, toxic reactions. Smith[1] has pointed out that, while infant mortality in the United States decreased each year from 1952 to 1956 to a low of 26.0 per thousand, it rose in 1957 to 26.4 and again in 1958 to 26.9. The reasons for these increases are not known, and presumably part of this mortality is the result of neonatal staphylococcal and other infections as well as respiratory distress associated with pulmonary hyaline membranes. However, the possibility that some of this increased mortality is iatrogenic is sufficient to suggest extensive review of therapeutic practices, particularly those employed in the management of newborn and premature infants. Altered responsiveness to infectious agents as a function of the age of the host is common pediatric knowledge.[2] It is the purpose of this review to examine the evidence for different responses to pharmacologic agents that are attributable to the age or maturity of the patient.

The response to a drug, whether a therapeutic or a toxic response, is the result of the interaction of a number of factors, any or all of which may vary with age. Since there are threshold levels below which most compounds are inactive, most of the factors under consideration determine whether or not there is a response. They do not alter the character of the response once it occurs. Abnormal responsiveness is usually invoked in the presence of a toxic response to a drug in dosage which was expected to be quite safe. The *size* of the

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individual is one factor which determines the concentration of the drug, at least in the total individual, and the variables of *weight* and *surface area* used to calculate pediatric doses express an appreciation of the total volume through which an administered compound is distributed and the influence of this factor on the ultimate concentration of a drug at a receptor site. Alterations in the rate and efficiency of *absorption* or of *excretion* of drugs could also alter effective concentrations. Similarly, barriers to or facilitation of *distribution* to certain areas could produce abnormal responses. It is possible that in individuals of different ages and experience the same concentration of a drug at a receptor site could evoke different responses. Differences in the *metabolism* or *detoxification* of drugs appear intuitively to be particularly fruitful areas in which to search for and to explain differences in responses to drugs, particularly in the neonatal period. In the course of human development changes occur simultaneously in many of these biologic variables, so that there are probably multiple causative elements in the adverse responses of any age group. It seems useful therefore to consider those instances in which evidence of an altered response to a drug has been documented; to discuss information relating to the reasons for the altered response where this is available; and to attempt to see general principles when this is possible. Data bearing on responses in the human will be emphasized, since those situations in which clinical toxicity has been observed deserve particular scrutiny. Pertinent observations made on experimental animals will be considered where information on man is not available. Clinical observations which led to the recognition of the toxic response will be considered in some detail, for it is felt that current examples may serve as models for the recognition of others. Clinical therapeutic implications will be discussed wherever possible. Speculation will be employed when it suggests further research.

An outline of the topics which will be considered follows:

- Neonatal toxicity associated with the failure of development of enzyme systems during an interval postnatally
  - Toxic responses to chloramphenicol in newborn and premature infants
    - Introduction
    - Recognition of the syndrome
    - Clinical features
    - Physiologic and biochemical aspects
    - Enzymology and development
    - Implications
  - Inefficient glucuronidation as a factor in the toxicity of other drugs
  - The late development of other enzyme systems used for the metabolism of drugs
    - Microsomal oxidative systems
    - Succinylcholine and pseudocholinesterase
    - Acetylations
- Enzyme, substrate, cofactor interactions
  - The toxicity of vitamin K in newborn and premature infants
    - Recognition and clinical syndrome
    - Animal experiments; vitamin E
    - Metabolic defect in the red blood cell; glutathione stability
    - Clinical implications
- Influence of the size of the patient on responses to drugs
  - Inadvertent overdosage; streptomycin toxicity following the use of penicillin-streptomycin combinations
  - Correction for the size of the patient
- Absorption and excretion
  - Renal factors

Toxic effects related to systems for distribution
Sulfonamides and kernicterus
Permeability effects in distribution
Altered cerebral metabolism in the newborn
The retina
Hepatic function; anabolic steroids
Mechanisms of unexplained type; atropine
General conclusions
Summary

NEONATAL TOXICITY ASSOCIATED WITH THE FAILURE OF ENZYME SYSTEMS TO DEVELOP DURING AN INTERVAL POSTNATALLY

Toxic responses to chloramphenicol in newborn and premature infants. The relative ease with which infants in the first weeks of life develop overwhelming bacterial infections and the relative paucity of clinical findings indicating the presence of these infections[3] have led to widespread use of prophylactic antibiotic therapy in nurseries. Premature infants and infants born following premature rupture of the membranes are the groups most commonly managed in this manner. In addition, careful pediatricians initiate investigation and therapy for neonatal septicemia on the basis of minimal indications. Infections in the newborn which would be considered minor in another age group are often treated with vigorous antibiotic therapy. Chloramphenicol has commonly been employed for these purposes because of its broad antibacterial spectrum and its usefulness in the treatment of severe infection due to certain of the organisms producing neonatal infections. Recognition of a syndrome of chloramphenicol toxicity in newborn and premature infants represents the results of careful clinical observation in a group of patients in whom unexplained death is common.

Recognition of the syndrome. Three reports which appeared within a short period of time made a strong case for the existence of such a syndrome. Sutherland[4] reported 3 cases of full-term newborn infants whose deaths in peripheral vascular collapse appeared to be related to the administration of large doses of chloramphenicol. A small number of deaths in vascular collapse during chloramphenicol therapy had previously been reported, but the coexistence of disease such as typhoid fever rendered interpretation difficult. In none of Sutherland's patients was severe infection noted clinically or at autopsy: 2 were born after premature rupture of the maternal membranes; one of these developed periumbilical erythema; and the third was treated in response to abdominal distention and poor feeding. They died between the fifth and seventh day of life following doses of chloramphenicol which seem quite large. Two received intramuscular injection of the microcrystalline suspension in doses of 220 and 230 mg. per kilogram per day for 60 and 72 hours, respectively, while the other patient received 50 mg. per kilogram per day of the palmitate ester for 56 hours and a single inadvertent dose of 400 mg. On the other hand, Kent and Wideman[5] observed the same syndrome following more conventional doses of the antibiotic. Their patients, a mixed group of premature and full-term newborn infants, received 100 to 300 mg. of chloramphenicol per day as prophylaxis following premature rupture of the membranes. The mortality rate of infants born after premature rupture of the membranes rose significantly from 29 per 1,000 in 1954 when prophylactic antibiotics were not used to 144 per 1,000 in a group of patients receiving prophylactic antibiotic therapy in 1958. This latter rate represents 23 patients who died out of 160 who received prophylactic antibiotic therapy. All of those who died received chloramphenicol, as did 8 additional patients who survived although they presented the same clinical picture. A controlled clinical study of prophylactic antibiotic therapy carried out by Burns, Hodgman, and Cass[6] in premature infants born more than 24 hours after rupture of the membranes provided more definitive evidence of an unusual responsiveness of the newborn to this antibiotic. The chloramphenicol-treated patients in this study received 100 to 165 mg. per

Table I. Mortality of infants on various regimens of prophylactic antibiotic therapy*

Birth weight (grams)	*Group 1 (No treatment)*		*Group 2 (Chloramphenicol)*		*Group 3 (Penicillin and streptomycin)*		*Group 4 (Penicillin and streptomycin and chloramphenicol)*	
	Total infants	*% who died*	*Total infants*	*% who died*	*Total infants*	*% who died*	*Total infants*	*% who died*
<1,000	1	100.0	0	0	3	100	1	100
1,001-1,500	5	40.0	5	100	2	0	4	100
1,501-2,000	9	22.0	9	67	4	75	11	90
2,001-2,500	17	5.9	16	50	24	0	15	40
Total	32		30		33		31	
Averages		19.0		60		18		68

*Data of Burns, Hodgman, and Cass.[6]

kilogram per day. The data (Table I) provide little support for those who advocate the use of prophylactic antibiotic therapy in these situations. The mortality in the group of patients treated with penicillin and streptomycin was almost identical with that of the group of untreated controls. In the two groups in which chloramphenicol was used, significantly higher mortality rates were observed.

Clinical features. A characteristic clinical picture has been described in the cases reported. Symptoms began 2 to 9 days after the beginning of administration of chloramphenicol with failure to feed or vomiting. Shortly thereafter the onset of shallow irregular respirations was observed. Abdominal distention and loose stools were described in one of the reports. Progression of symptoms was very rapid, in the 12 to 24 hours after their onset, leading to the fully developed syndrome of ashen, gray cyanosis, hypothermia, and flaccidity followed shortly by death, which has uniformly been interpreted to represent cardiovascular collapse. Postmortem examination has failed to reveal morphologic signs of toxicity.

Physiologic and biochemical aspects. The structure of chloramphenicol (Fig. 1) provides a number of functional groups with which one might associate toxicity. The nitrobenzene and dichloracetyl moieties suggest themselves immediately. Yet the formation of the glucuronide, leaving these groups unaltered, yields a compound that is relatively nontoxic.[7] The glucuronide is considerably more soluble in water than is free chloramphenicol, so that detoxification in this way may represent more than removal of a functional group. Dehalogenation of chloramphenicol also reduces its toxicity for mammals and microorganisms.[7] Reductive formation of aryl amine derivatives is apparently not a major metabolic pathway in man. The mechanism of the toxic manifestations is not clear, but experimental animals given lethal doses of chloramphenicol develop respiratory depression and a fall in blood pressure.[8]

In early studies of the metabolism and excretion of chloramphenicol Glazko and colleagues[9] demonstrated that in the adult human 90 per cent of an oral dose is excreted in the urine in the first 24 hours after administration and that less than 10 per cent of this is active, unaltered chloramphenicol. The major metabolic product was found to be the glucuronide[10] (Fig. 1). Free chloramphenicol is excreted by glomerular filtration, whereas the glucuronic acid conjugate is secreted by the renal tubule.[9] Immaturity of renal function may contribute to the development of the syndrome under discussion, for Weiss, Glazko, and Weston[7] observed that in newborn infants the total urinary excretion of chloramphenicol and its products in 24 hours accounted for less than half of the dose. Colorimetric assay for total nitro compounds provided evidence of very high blood levels in infants who died of chloramphenicol toxicity[6] (Fig. 2). It has now been carefully documented[7] that infants in the first week of life develop considerably higher blood levels than do older infants

or children following the same dose of chloramphenicol, and that in the younger infant levels are maintained for longer periods of time. With repeated dosage, levels may rise progressively as illustrated. These observations could be consistent with a renal explanation. However, the amount of free chloramphenicol excreted in the urine of infants did not differ from values found in adults. Furthermore, examination of the blood of infants revealed that approximately 65 per cent of the total nitro products circulate in the form of free chloramphenicol. Anuric adult patients given chloramphenicol accumulate high blood levels of total nitro compounds; but very small levels of the active drug remain, and its half life is not prolonged.[11] These observations indicate that renal mechanisms do not account for the different responses to chloramphenicol in infants and adults, and they serve to focus attention on the mechanisms by which the inactive glucuronide is formed.

Enzymology and development. It is now known that the carbon skeleton for glucuronidation is provided by glucose, that a number of enzymes are involved in this conversion, and that uridine nucleotides are intermediates[12*]:

$$\text{G-1-P} + \text{UTP} \xrightleftharpoons{\text{UDPG pyrophosphorylase}} \text{UDPG} + \text{PP}$$

This enzyme is one of a group of PP uridyl transferases and is often called by that name.

$$\text{UDPG} + 2\ \text{DPN}^+ \xrightleftharpoons{\text{UDPG dehydrogenase}} \text{UDPGlucuronic acid} + 2\ \text{DPNH} + 2\text{H}^+$$

$$\text{UDPGlucuronic acid} + \text{ROH} \xrightleftharpoons{\text{glucuronyl transferase}} \text{R-glucuronide} + \text{UDP}$$

The UDP formed in the third reaction can be rephosphorylated in the presence of ATP to UTP. The dehydrogenase is a soluble enzyme, while the glucuronyl transferase is in the microsomes. In addition to conjugation with hydroxyl groups as in the case of chloramphenicol, glucuronic acid conjugates are formed with amino and carboxyl groups. A number of compounds of biologic importance are conjugated with glucuronic acid, including thyroxine, tetrahydrocortisone, and bilirubin. The development of some of these enzymatic mechanisms was studied by Brown and Zuelzer[13] in the course of studies on the hyperbilirubinemia of the newborn. The acceptors used were *o*-aminophenol or phenolphthalein, and UDPGA was the donor in systems containing microsomes from livers of fetal, newborn, and adult guinea pigs. It was found that glucuronyl transferase activity was virtually absent in the fetal liver and markedly reduced in that of the newborn. Over the first 15 to 20 days of postnatal life an approximately fivefold increase occurred, to levels of enzyme activity approximating those found in adults. These investigators also found that the activity of UDPG dehydrogenase was very low in fetal and newborn liver and increased gradually to adult levels over the first 2 weeks of life. That these important observations reflect deficient conjugation on the part of the newborn in vivo has been shown by the work of Vest,[14] who administered acetanilid to newborn infants and to older infants and children. This compound is oxidized in adults to N-acetyl-*p*-aminophenol and then conjugated with glucuronic acid. The absorption of acetanilid and its oxidation did not appear to be altered in the newborn infants, but their ability to conjugate the

*The following abbreviations have been used:
G-1-P, glucose-1-phosphate; UTP, uridine triphosphate; UDPG, uridine diphosphoglucose; PP, inorganic pyrophosphate; DPN^+ and DPNH, the oxidized and reduced forms of diphosphopyridine nucleotide; UDP, uridine diphosphate; ATP, adenosine triphosphate; UDPGA, uridine diphosphoglucuronic acid; GSH and GSSG, the reduced and oxidized forms of glutathione; TPNH, reduced triphosphopyridine nucleotide.

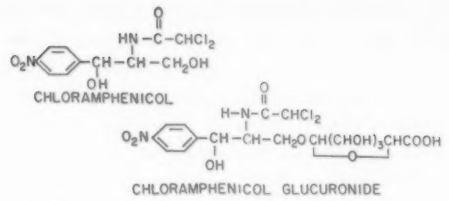


Fig. 1.

resulting phenol with glucuronic acid was markedly reduced.

Implications. The observed deficiency in the newborn of enzyme systems capable of conjugating chloramphenicol is consistent with the production of significantly higher levels of free, active chloramphenicol in the blood of the newborn when compared with that of the older child following the same dose. It is similarly consistent that the clinical picture seen in infants given doses which are conventional for older children is the same as that which follows the administration of much larger doses to adult animals. The practical implication of these findings for the use of chloramphenicol is that smaller doses should be employed. It has been recommended[7] that the maximum daily doses for full-term and premature infants be 50 and 25 mg. per kilogram, respectively, during the first month of life. Toxic manifestations have not been observed with these doses, but adequate blood levels can be achieved in the majority of full-term newborn infants in the first week with 25 mg. per kilogram. It seems likely that these experiences will tend to decrease the widespread use of this antibiotic in this age group and that this and other experiences may lead to a questioning of the practice of administering prophylactic antibiotic therapy at this time of life. Where chloramphenicol appears to be the drug of choice in the treatment of newborn or premature infants, it is possible that an average safe dose may in some cases result in toxic levels and in others may fail to produce therapeutic levels. The safest course would seem to be to monitor dosage by the determination of the levels of the drug in the blood.

Inefficient glucuronidation as a factor in the toxicity of other drugs. Disclosure of the toxicity of chloramphenicol in the newborn infant has broad significance, since it suggests that similar toxicity may result from other drugs which are detoxified in the adult by glucuronidation, and for which toxic and effective doses have been determined only in adult animals. Acetanilid is seldom administered to the newborn, and a wide margin of safety would be expected for thyroxine or hydrocortisone until the enzymes required have developed. However, the mechanism of detoxification is a widespread one. Glucuronide formation occurs, for instance, in the catabolism of morphine,[15] and newborn rats have been found to succumb to much smaller doses of morphine than have adult ones.[16] Progesterone has been found to be unusually toxic in the neonatal period. Karnofsky and colleagues[17] reported that the LD_{50} in mice rose forty-fold above adult levels in the first 7 days of life. Whether or not this is related to inefficient glucuronidation of progesterone is a subject for further research. Isolated instances of toxicity might escape notice, whereas further examples of specialized toxicity might be expected to be observed with the development of a new drug or the novel application of an old one in the management of a large number of infants.

The late development of other enzyme systems used for the metabolism of drugs. The toxicity of chloramphenicol in the newborn is of even more general significance in that it illustrates the principle that infants may be particularly vulnerable to the toxic action of drugs during a postnatal period in which the enzymes required for drug metabolism are developing. Although there are as yet not many examples of this phenomenon, it could be quite general, for the activity of a number of enzymes has been found to be very low in the newborn and to develop or increase postnatally. This pattern will undoubtedly be observed in the study of other enzymes. The development of enzyme systems has been the subject of a number of recent reviews.[18-20] Differences

in the activity of an enzyme between newborn and older animals could represent: absence of the enzyme protein; deficiency of cofactors; the presence of an enzyme in the young with properties different from those in the older animal; or the presence of inhibitors in the newborn.

Microsomal oxidative systems. Fouts and Adamson[21] have presented evidence that a number of drugs which in the adult are metabolized by enzymes contained in the microsomes of liver are not metabolized by the livers of newborn rabbits. The reactions studied were the oxidation of the side chain of hexobarbital, N-dealkylation of aminopyrine, deamination of amphetamine, hydroxylation of the aromatic ring of acetanilid, oxidation of the ring sulfur of chlorpromazine, and reduction of the aromatic nitro group of *p*-nitrobenzoic acid. The liver of the newborn was unable to metabolize any of these drugs. Gradual development of enzyme activity occurred over the first weeks of life, so that by 4 weeks of age adult levels were observed. Similar evidence of immaturity of the microsomal systems involved in the metabolism of many drugs was observed by Jondorf, Maickel and Brodie,[22] who studied the systems that N-demethylate monomethyl-4-amino-antipyrene and aminopyrine dealkylate phenacetin and oxidize the side chain of hexobarbital. These investigators found that the livers of newborn guinea pigs lacked the systems for carrying out these conversions in vitro, and that by 8 weeks of age adult levels were present. They also reported experiments carried out in vivo which indicate that newborn mice do not metabolize aminopyrine, phenacetin, or hexobarbital. Evidence of altered pharmacologic effects were also obtained, for prolonged sleeping time was produced in the newborn with a dose of hexobarbital which had little effect on adult mice. Evidence that there might be an inhibitor of amphetamine metabolism in the liver homogenate of newborn rabbits was reported by Fouts and Adamson.[21] Similar results were obtained with three of the other drugs studied, but no inhibition was demonstrable in the case of nitrobenzoic acid or chlorpromazine, so that more than one mechanism may be involved. In contrast to these data the experiments of Vest[14] indicated that the newborn human infant readily carries out the oxidation of acetanilid to N-acetyl-*p*-aminophenol. The deficiency of such a large number of metabolic systems in the newborn rabbit, mouse, and guinea pig and the parallel changes in activities in the first weeks of life suggest that synthesis or unmasking of the enzymes is initiated by a single event.

Succinylcholine and pseudocholinesterase. Prolonged apnea following the use of succinylcholine as an anesthetic adjunct during operation has been reported by Kaufman, Lehmann, and Silk.[23] The infant was found to have a low level of serum pseudocholinesterase, and concomitant inability to metabolize succinylcholine is consistent with the abnormal pharmacologic response. The case reported is thought to be an example of genetic deficiency of pseudocholinesterase, although assay of the enzyme in the parents did not support this conclusion, for Kalow and Staron[24] have shown that determination of this enzyme in the serum does not segregate the heterozygote. Determination of the

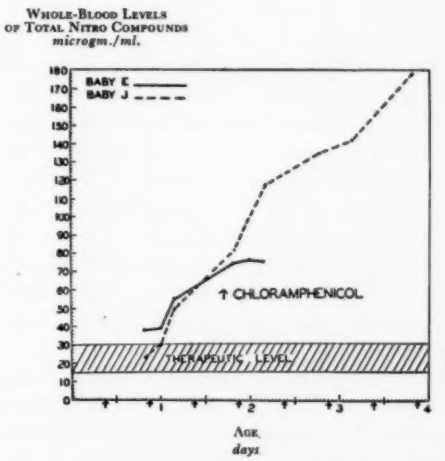
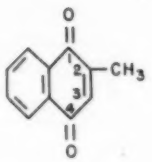
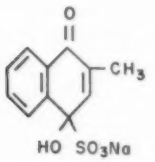


Fig. 2. Concentrations of chloramphenicol in the blood. Data of Burns, Hodgman, and Cass.[6] Both infants died within 4 hours of the last value indicated.



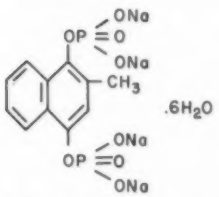
MENADIONE

(2-Methyl-1, 4-Naphthoquinone)



MENADIONE SODIUM BISULFITE

(HYKINONE^R)



SODIUM MENADIOL DIPHOSPHATE

(SYNKAYVITE^R)

Fig. 3.

inhibition of this enzyme by dibucaine clearly distinguishes three populations which appear to express normality, heterozygosity, and homozygosity for this defect. On the other hand, newborn infants have abnormally low levels of pseudocholinesterase[25] and could therefore react adversely to succinylcholine. Determination of the degree of inhibition of this enzyme by dibucaine in a large number of newborn infants would be of interest.

Acetylations. Acetylation constitutes the major metabolic fate of a number of compounds containing free amino or related groups. The best known examples of this process are the sulfonamides. Limited ability to acetylate sulfonamides has been observed in newborn and premature infants by Fichter and Curtis.[26] A relatively high proportion of circulating free sulfonamide could increase the therapeutic effectiveness of a given dose in these infants for the acetylated product is without antibacterial activity. On the other hand, there is no evidence that acetylated sulfonamides are less toxic than the unconjugated compounds, and their decreased solubility in water tends to promote renal complications. Failure to acetylate efficiently does not, therefore, seem to increase the susceptibility of the infant to sulfonamide toxicity, but this evidence of metabolic immaturity could promote the toxicity of other compounds which are inactivated by acetylation. Isonicotinic acid hydrazide (isoniazid, INH) is excreted almost quantitatively as the acetyl derivative,[27] and acetylation of this compound appears to decrease its toxicity for animals as well as for tubercle bacilli. Genetic deficiency in the acetylation of isoniazid has been reported,[28] but information as to the ability of the newborn infant to carry out this transformation is not available.

ENZYME, SUBSTRATE COFACTOR INTERACTIONS

The toxicity of vitamin K in newborn and premature infants.

Recognition and clinical syndrome. The capacity of 1,4-naphthoquinones to produce hemolytic toxicity has been known almost as long as has their vitamin K activity.[29] However, the very large amounts of the menadione (2-methyl-1,4-naphthoquinone) (Fig. 3) derivatives required to produce toxic effects in adult animals[29, 30] and the very small doses required to prevent or reverse hypoprothrombinemia suggested that the therapeutic index was sufficiently large that the compounds were essentially nontoxic. The water-soluble derivatives of menadione, including the sodium bisulfite salt (Hykinone) and the tetrasodium salt of the diphosphate ester (Synkayvite) (Fig. 3), have received widespread clinical use. The practice of administering large doses to newborn and premature infants became popular recently, although its rationale is

not clear. Allison[31, 32] first called attention to the possibility that the administration of large doses of these compounds to premature infants could produce hemolytic anemia, jaundice, and kernicterus; and Laurance[33] observed an increase in the incidence of kernicterus in a premature nursery following an increase in the dosage of a vitamin K preparation routinely administered. The occurrence of Heinz bodies in the erythrocytes of affected infants was noted by Willi.[34, 35]

Among the patients described, nearly all have been premature infants, and the blood smears observed at birth have been normal. Administration of a water-soluble vitamin K preparation, in dosage of at least 30 mg., has been carried out as a routine procedure or, less commonly, in response to some hemorrhagic manifestation. Large numbers of Heinz bodies have appeared over the next few days. These have then disappeared and anemia has progressively increased over the following 2 weeks. Maximal icterus has been found at 1 to 2 weeks of age. Although signs of anemia have been observed in some of these patients, the predominant manifestation has been kernicterus. Crosse, Meyer, and Gerrard[36] carried out a retrospective survey of premature infants with kernicterus. Of 60 infants who did not develop kernicterus, only 2 received more than 50 mg. of vitamin K, while 13 of 60 who did develop kernicterus received more than 50 mg. The yearly incidence of kernicterus during a period when the total dose of vitamin K was 1 to 2 mg. varied from 0.5 to 2.1 per cent and increased to 4.1 and 3.6 per cent in 2 years in which the total dose was over 30 mg. Studies carried out by a number of investigators[37-39] have shown that the administration of 30 mg. of sodium menadiol diphosphate produces levels of bilirubin in the serum of both full-term and premature infants that are significantly higher than those of controls. Untreated controls did not differ from those who received a 1 mg. dose. Vitamin K_1 (Mephyton) did not alter the serum bilirubin concentration.[39] Experience with a small group of patients has been reported by Lucey and Dolan[40] which suggests that hyperbilirubinemia and kernicterus can also be produced in the infant by the administration of large doses of water-soluble vitamin K preparations to the mother during labor.

Animal experiments; vitamin E. The mechanism by which menadione produces hemolysis is not known, but the problem has been extensively explored, and it is probable that multiple factors are involved. The compound itself appears to be toxic to erythrocytes in the peripheral blood, for Synkayvite induces Heinz body formation in vitro.[34] Hemolysis and hemoglobinuria were produced by Allison, Moore, and Sharman[41] in vitamin E–deficient rats. The same doses of menadione were without effect on control rats or on rats receiving the deficient diet and supplementary α-tocopherol. This picture has been produced by all of the water-soluble preparations of vitamin K studied.[41-42] Vitamin K_1 did not produce hemolysis with or without vitamin E deficiency. These experimental observations have relevance to the particular sensitivity of the newborn to the hemolytic effects of menadione, for there is a considerable body of evidence indicating that the levels of vitamin E in the newborn are markedly lower than those of children and adults.[43-46] Furthermore, the greater incidence of this complication in premature infants than in those born at term is consistent with the prolonged persistence of low levels of vitamin E in the serum of premature infants fed partially skimmed cow's milk mixtures.[45, 46] In contrast, the levels of tocopherol in the serum rose promptly to levels in adults in the first week of life in breast-fed full-term infants and somewhat slower in those fed whole cow's milk mixtures.

Metabolic defect in the red blood cell; glutathione stability. The production of Heinz bodies in the erythrocytes and hemolytic anemia has been observed with a large number of chemical agents[47, 48] including compounds like acetylphenylhydrazine, classically associated with this function, as well as compounds similar to

menadione such as naphthalene itself. A number of reports have appeared[49-51] in which hemolytic anemia in the newborn infant has been associated with naphthalene. On the other hand, a defect in erythrocyte metabolism, in which there is an abnormal sensitivity to naphthalene, primaquine, and certain other drugs, has been shown to be genetically determined by Childs, Zinkham, and co-workers.[52] Erythrocytes from drug-sensitive individuals have a decreased content of reduced glutathione (GSH) and an altered GSH stability in that the concentration of GSH decreases sharply after incubation with acetylphenylhydrazine.[53, 54] These observations are consistent with earlier findings of an association between the content of reduced GSH and the integrity of erythrocytes.[55, 56] In this condition the activity of the enzyme glucose-6-phosphate dehydrogenase is deficient in the red blood cells,[57] and this is felt to be the direct expression of the abnormal gene. The alteration in GSH metabolism could be explained as a secondary effect, for the oxidation of glucose through this pathway results in the generation of reduced triphosphopyridine nucleotide (TPNH), and this compound is a cofactor for the enzyme glutathione reductase which catalyzes the generation of GSH from its oxidized form GSSG. With these observations in mind Zinkham[58] has studied the erythrocytes of newborn infants. The concentration of GSH was found to be normal or elevated in these subjects. However, a marked decrease in concentration followed incubation of the cells with acetylphenylhydrazine. The addition of α-tocopherol in vitro did not alter the abnormal GSH stability test. On the other hand, direct measurement of the activity of glucose-6-phosphate dehydrogenase failed to reveal evidence of deficiency of this enzyme in the newborn. In an attempt to explain this discrepancy between the genetically determined reactor and the newborn infant, it was found that the in vitro addition of glucose to the blood of the newborn prevented the abnormal GSH stability test. As can be predicted from the nature of the defect, no such protective effect could be obtained by addition of glucose to the blood of the reactor. These data suggest that altered GSH stability and concomitantly reduced erythrocyte integrity in the newborn result from a deficiency of glucose, as substrate for TPNH generating systems. Relative hypoglycemia has been observed in the newborn infant,[59-61] but one wonders if the differences observed in the levels of sugar in the blood which are relatively small when compared with those required in vitro are responsible for the marked, almost qualitative differences in GSH stability. The addition of menadione sodium bisulfite to the blood of the newborn produced a sharp decline in the levels of GSH, similar to that produced by acetylphenylhydrazine, and the levels of glucose declined in parallel fashion. However, incubation of the blood of normal newborn infants without added compounds resulted in a similar fall in glucose concentration without change in GSH. Thus, glucose concentration appears to be related to the mechanism of hemolysis of the neonatal erythrocyte by menadione as does tocopherol deficiency, but the degree of interrelation of the observed abnormalities and the mechanism of the hemolysis is not clear.

Clinical implications. It is important for considerations of general clinical manage-

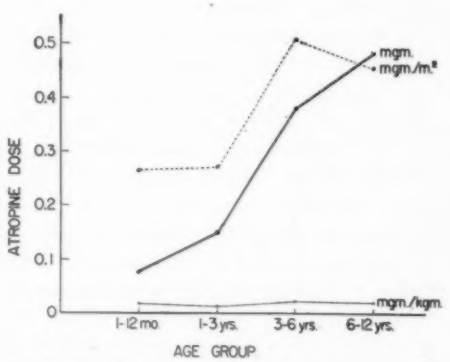


Fig. 4. Dose of atropine required to depress salivation in various age groups. Data of Unna and coworkers.[71] The minimal effective dose was determined for each subject and the means for each age group have been plotted.[72]

ment to emphasize that these adverse reactions occurred following the administration of very large doses of vitamin K preparations, in excess, and occasionally considerably in excess, of 30 mg. to infants weighing approximately 2 kilograms. Hyperbilirubinemia was not produced by doses in the range of 1 mg.[38, 39] Yet, doses of 0.5 to 1.0 mg. are effective in the prevention or treatment of the hypoprothrombinemia of the newborn.[62, 63]

INFLUENCE OF THE SIZE OF THE PATIENT ON RESPONSES TO DRUGS

Inadvertent overdosage; streptomycin toxicity following the use of penicillin-streptomycin combinations. The recent occurrence of a number of examples of toxicity to the central nervous system in young infants following the use of preparations combining streptomycin and penicillin has resulted in federal requirements that manufacturers of such combinations include on package inserts the comment: "Not for pediatric use."[64, 65] The major toxic manifestation has been prolonged coma, beginning within 30 minutes of administration and lasting as long as 6 to 8 hours. A few deaths have been observed. These patients received doses of 0.5 Gm. of streptomycin. This quantity of streptomycin is contained in a volume containing 300,000 to 400,000 u. of penicillin, doses of penicillin which are commonly employed with safety in the infant. However, a 3 kilogram infant receiving such a dose receives over 150 mg. per kilogram of streptomycin. It is possible that the infant reacts in a special way to streptomycin, but the recent data of Alfred and Sutherland[66] indicate that newborn and adult rats react similarly to this antibiotic and these considerations suggest that the infants discussed simply received too much streptomycin because of its presence in a mixture of antibiotics. This illustrates the danger of combinations of antibiotics; their use in pediatrics is generally difficult to justify. It also indicates the necessity for adjusting the doses of drugs used in adults by factors for the size of the patient in determining pediatric doses. This has constituted the subject of most previous discussions of pediatric pharmacology.

Correction for size of the patient. The correction most generally employed in clinical pediatrics as well as in experimental pharmacology is a simple correction for the body weight in kilograms. Clark's rule, which is a correction for body weight, is almost never invoked by the pediatrician, and the rules of Young and Cowling, which depend on the age of the child, appear even less useful. The aim of these methods is to obtain standardization of dosage, such that a single dosage may be used for the infant, child, and adult. The expression of doses in grams or milliliters per square meter of body surface has been proposed for this purpose, and, in support of this thesis, Crawford, Terry, and Rourke[67] have reported apparent linearity for the relationship between blood concentrations of salicylate or sulfadiazine and dosage expressed as grams per square meter. In consideration of this proportionality it is useful to recall that Adolph[68] accumulated a diverse body of data from many mammalian species, which indicated that physiologic processes as well as anatomic details are accurately described as power functions of body weight. The general equation is $P = aW^k$, or $\log P = \log a + k \log W$ in which a and k are numerical constants that express the relationship between weight (W) and the particular parameter (P) under study. Surface area may be expressed as $7.1 \times W^{.71}$, an approximately ⅔ power function of weight. This is a power function with which physiologists are familiar and comfortable, and, although most individuals are completely comfortable only with a power function of 1.0, this may account for some of its popularity. Forbes[69] has recently pointed out that the mathematical expression of the fractional powers of any series of numbers greater than one results in a series of numbers that are less variable than the original numbers. Thus a decrease in the variability of data when plotted against body surface as opposed to body weight may re-

flect only the nature of the mathematical transformation. Furthermore, a wide variety of power functions were required to express some physiologic processes,[68] and it would not be surprising if pharmacologic responses represented an even more variable spectrum. The doses of some drugs may be approximately proportional to a ⅔ power of the body weight, but each drug or class of drugs may best be represented by some other power function. Working with the hypothesis that it was rational to permit the data obtained to determine these relationships with a minimum of a priori assumptions, Bliss, Greiner, and Gold[70] found that the threshold dose of digitoxin required to produce changes in the electrocardiogram of human subjects increased linearly with the square root of the body weight in pounds. Unna and colleagues[71] studied the relationships of age and size and the response of human subjects to atropine. These investigators determined the threshold dose required to suppress salivation at various ages. Their data for the mean effective doses of atropine have been expressed graphically[72] (Fig. 4). There was an approximately sixfold increase in absolute dosage with age. The increase was less marked when the data were expressed on the basis of body surface. Expression of the dose in milligrams per kilogram resulted in essentially a single dose for all of the age groups studied. Thus, in this case a power function of 1.0 most closely described the data. Unfortunately, careful studies of the responses of significant numbers of infants, children, and adults to pharmacologic agents is rare, for the implication is that the relationship between size and drug dosage is better determined than expressed by any universal constant. Furthermore, sufficient data have already been presented to indicate that the responses of the newborn infant to drugs are often special. None of the studies quoted in this section reflect the peculiar responses of the newborn infant. These responses must also be determined, for linearity of response in older infants and children may not safely be extrapolated to the neonatal period.

ABSORPTION AND EXCRETION

Renal factors. The absorption of small molecules from the gastrointestinal tract has not been extensively studied at different ages, but there is no evidence of increased absorption in the very young which would promote toxic effects. Furthermore, parenteral administration is particularly common in infancy, limiting variability attributable to the absorption of drugs. On the other hand, there is a large body of data which indicate that renal function is immature in the very young infant. Histologic examination has provided evidence for postnatal development at least in the premature infant in the number of glomeruli[73] and in the form of the glomerulus[74] during the first 2 years of life. Studies of renal physiology have indicated that the tubules as well as the glomeruli are immature in the infant.[19, 75-78] The glomerular filtration rate in young infants has been found to be 30 to 50 per cent of adult values, with the lowest values in small premature infants. The effective renal plasma flow, as measured by the clearance

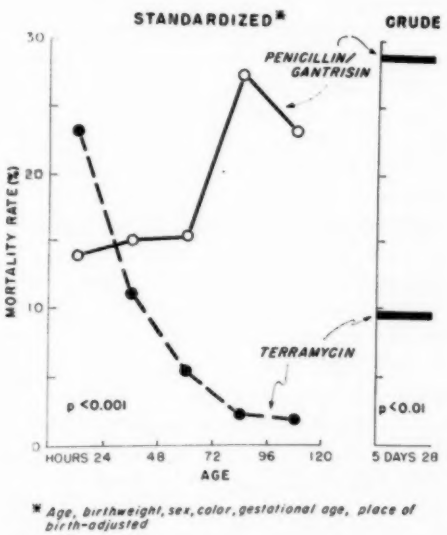


Fig. 5. Mortality rates by age. Data of Silverman and associates.[81] Differences between the two treatment groups were not significant during the first 47 hours. Thereafter differences were significant.

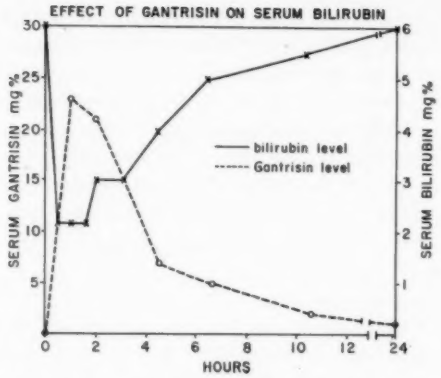


Fig. 6. Concentration of bilirubin and of sulfisoxazole in the serum following a dose of the sulfonamide. Data of Johnson and collaborators[84] obtained in rats of the Gunn strain.

of Diodrast or *p*-aminohippuric acid (PAH), approximated 20 to 40 per cent of that of the adult. In contrast to the histologic findings, the tubular functions were proportionally lower than those of the adult, so that the filtration fraction, which in adults and children past infancy is 0.2, was found to be 0.3 to 0.4 in young infants. Barnett[78] suggested that ratios of the clearance of inulin to the T_M for PAH indicate that glomerular function is more highly developed than tubular function in infancy. Renal function in the very young infant is also characterized by a lowered T_M for glucose, imperfect mechanisms for regulation of acid base equilibrium, and lowered clearances of sodium, chloride, and potassium. Although complete maturity may not be achieved until a year of age or later, maximum tubular concentrating power appears within the first 2 months of life.[79] The pharmacologic implications of these observations have not been extensively studied. Barnett and co-workers[80] found that the clearance of penicillin, like the clearance of inulin, was in the adult range in a group of children from 2 to 12 years of age. On the other hand, in a group of premature infants, the clearance of penicillin was reduced to 17 per cent of the value obtained in children over 2 years of age. These data indicated that the administration of the same number of units of penicillin per unit of surface area would result in significant blood levels in the infant for six times as long as in the older children, and for three times as long for doses calculated on the basis of weight. It is probable that the high levels of chloramphenicol previously discussed[6, 7] were influenced by the renal function of the infants studied. However, data obtained with older subjects indicated that if detoxication mechanisms are normally present this compound may be safely handled by the anuric patient. Inefficient renal excretion of sulfonamides in newborn and premature infants appears to contribute to the unusually high levels observed by Fichter and Curtis[26] in newborn and premature infants. However, clinical evidence of drug toxicity in the newborn on this basis is not available. It seems likely that the immature renal function of the very young infant is one of many factors that may contribute to unusual toxic responses in this age group. More of these factors will be recognized as they are more carefully sought.

TOXIC EFFECTS RELATED TO SYSTEMS FOR DISTRIBUTION

Sulfonamides and kernicterus. The association between the administration of sulfonamides to premature infants and an unusual incidence of kernicterus illustrates the value of the careful, controlled clinical trial in bringing to light new syndromes of this sort, as well as in evaluating empirically accepted or new therapeutic regimens. The study in which this association was made was designed by Silverman and colleagues[81] to compare two prophylactic antibacterial regimens in the therapeutic management of premature infants. One group received oxytetracycline and the other, penicillin and sulfisoxazole (Gantrisin diethanolamine). An unexpected difference in mortality was observed (Fig. 5). The groups were not significantly different during the first 47 hours. The differences in mortality observed thereafter were significant. Kernicterus was found at necropsy nearly ten times more frequently in the group who received penicillin and sulfisoxazole. Most of those who died of kern-

icterus were observed to have peak levels of bilirubin in the serum of less than 15 mg. per 100 ml. Detailed study of the course of the serum bilirubin levels on the two regimens revealed that the levels were considerably lower in the group receiving penicillin and Gantrisin.[82] Previous and general experience with penicillin focused attention on sulfisoxazole as the agent responsible for the increased incidence of kernicterus and decreased concentrations of bilirubin in the serum. Similar observations were made by Johnson and colleagues[83, 84] in studies of rats with a genetic deficiency of glucuronyl transferase. Treatment of these rats with sulfisoxazole or sulfadiazine resulted in a marked increase in deaths and consistently lower serum bilirubin concentrations (Fig. 6). At necropsy, however, there was increased staining by bilirubin of the brain, subcutaneous tissue, and fat. The experiments of Odell[85, 86] have provided an explanation for these clinical and experimental observations. It was found in in vitro experiments that sulfisoxazole competed effectively with bilirubin for binding sites on serum albumin, displacing protein-bound bilirubin, and permitting dialysis or ultrafiltration through membranes which retain the protein-bound pigment. It appears that the lowered bilirubin levels found in the serum of rats or infants after the administration of sulfisoxazole is due to the displacement of bilirubin from attachment to the serum proteins, which promotes its diffusion into tissues. This competitive effect of sulfisoxazole is not specific for that molecule, but a general attribute shared with a number of organic anions, including other sulfonamides, salicylates, and caffeine sodium benzoate.

Permeability effects on distribution. The occurrence of kernicterus in the age groups under discussion as a result of the adverse effects of drugs as well as in the course of disease must also be influenced by factors of differential permeability, particularly by the efficiency of the barrier between the brain and the blood. Dyes such as trypan blue, present in the circulating blood, are not taken up by the adult brain, although the walls of capillaries and the choroid plexus are stained.[87] In the infant mouse, however, dye also enters the brain. Similar evidence of increased permeability from the blood to the brain in the neonatal period has been demonstrated with the use of the radioactive isotopes of phosphorus, chloride, and potassium in rabbits, rats, and chickens.[87] Himwich and Himwich[88] have reported that the brain of the infant rat is relatively permeable to glutamic acid, for administration of this compound resulted in an increase in its concentration in the brain during the first day of life. After 9 days, the concentration in the brain could not be increased by administration of the amino acid. The pharmacologic importance of this differential permeability is suggested by the work of Domek, Barlow, and Roth[89] who studied the distribution of C^{14}-labeled phenobarbital in the brains of cats at various ages using autoradiography. The penetration of phenobarbital into the brain of the kitten was more rapid than in the cat, and there appeared to be an inverse relationship between myelinization and drug concentration. These data could have relevance to the increased sensitivity to the toxicity of pentobarbital demonstrated in the infant rat by Etsten, Alexander, and Himwich[90] and to hexobarbital in the infant pig by Donald and Raventos.[91]

ALTERED CEREBRAL METABOLISM IN THE NEWBORN

It is also possible that this increased toxicity in the newborn reflects, at least in part, metabolic differences between the adult and the newborn either in specific systems for the metabolism of the drug or in metabolic factors of a more general nature. For example the increasing resistance to barbiturate toxicity observed over the first 2 to 3 weeks of life has been associated with a decreasing ability of the young animal to withstand the absence of oxygen.[92] These changes are correlated with developmental changes in the brain from a relative dependence on glycolytic to oxidative mechanisms as energy sources. Similarly, malonate, which inhibits

oxidations by inhibiting succinic dehydrogenase, is more effective on brain tissues after 10 days of life, while iodoacetate, which is primarily an inhibitor of glycolysis, is relatively more effective on the brain of the 1-day-old.[93] In contrast to the effects of most drugs, ethanol was found to be less toxic in the newborn than in the adult.[94]

THE RETINA

Developmental studies in ophthalmology have recently provided an interesting example of altered toxicity in the newborn animal. Lucas and Newhouse[95] demonstrated that repeated administration of sodium glutamate to neonatal mice induced a failure of development of the inner layers of the retina. This effect could also be produced by aspartate, but not by a variety of other compounds. These observations have been repeated by Potts,[96] who also noted that the failure of development of these cells resulted in a permanent disappearance of one of the two waves of the electroretinogram. Altered permeability could be a factor in these toxic effects of a normal metabolite, but the mechanisms involved in the production of these unusual lesions are not known.

It is not possible to leave a discussion of the retina of the newborn and exogenous toxic effects without recalling the association of retrolental fibroplasia and the administration of oxygen[97] as an example of the toxicity of a well-intended, generally accepted measure in the therapeutic management of premature infants.

HEPATIC FUNCTION; ANABOLIC STEROIDS

Impairment of the hepatic clearance of bromsulfalein has been reported as a toxic effect of two 17-substituted testosterone derivatives which have been used as anabolic steroids.[98, 99] This inhibition was not associated with structural abnormality and was completely reversible on withdrawal of the drug. Arias[100] has shown that the retention is due to an inhibition of mechanisms of transport from the liver cell to the bile. He found that the compound studied also lowered the maximal rate of excretion of bilirubin but did not inhibit UDPG dehydrogenase or glucuronyl transferase. Furthermore, the excretion of infused conjugated bilirubin was similarly inhibited. Evidence for toxicity in infants and children on this basis is not available, but anabolic androgenic steroids have been used in the management of premature infants, and it is possible that toxic effects of bilirubin could be produced in this way in the absence of systems for the efficient glucuronidation of bilirubin[101] and in the presence of hepatic excretory mechanisms which are already reduced.[102, 103*]

MECHANISMS OF UNEXPLAINED TYPE; ATROPINE

The subject of adverse pharmacologic responses peculiar to the newborn is related to the general subject that Gunn[104] has called cellular immunity, a term which does not represent antigen-antibody interrelations but designates congenital and acquired tolerance to nonprotein substances. The mechanisms of tolerance are not clear. However, study of the development of tolerance in the young animal in the course of normal development should provide information on the mechanism of these effects. Recent evidence has focused attention on the importance of the development of enzyme systems involved in detoxification, and information in this area will undoubtedly increase. Some of the other mechanisms responsible for altered responses in the young have been discussed in this review. It seems probable, however, that there are other factors involved which remain as questions for further research. This principle is illustrated by

*Recent observations of Sutherland and Keller suggest that the toxicity of novobiocin may be related to this system by which bilirubin is cleared into the bile.[102] These investigators noted an epidemic of jaundice in a newborn nursery to be associated with the administration of novobiocin. Michael and Sutherland[105] have found that in the rat the toxicity of novobiocin, tetracycline, and even penicillin is considerably greater in the newborn than in the adult. However, only in the case of novobiocin were the young rats noted to be yellow. Evidence has been presented[107] suggesting that the yellow pigment accumulating after novobiocin treatment is bilirubin and that the antibiotic may produce icterus by interfering with the excretion of bilirubin.

some work carried out by Clark[105] in 1912 on the toxic effects of atropine. Varying degrees of susceptibility to atropine in different species of rabbits have been associated with differences in the capacity of the liver to destroy the alkaloid, and among various species the relative resistance of rabbits and frogs to atropine is associated with the ability of tissues to metabolize it in vitro.[104] Clark observed that the liver and some other tissues of the frog and the rabbit were very effective in the destruction of atropine. On the other hand, the rat was even more resistant to atropine than either of these species; yet no tissues from the rat showed any ability to metabolize atropine. The very young rat is much more susceptible to atropine than is the adult. So that whatever factor accounts for the tolerance of the rat to this alkaloid develops postnatally. A group of children with atropine or homatropine toxicity were recently studied,[106] in whom the symptoms were predominantly those of central nervous system involvement. These toxic effects, however, do not appear to represent unusual responses to usual doses, but rather overdosage associated with the difficulties of administration of precise doses of eyedrops, including the technical aspects of administration and changes in concentration of solutions due to evaporation or errors in compounding.

GENERAL CONCLUSIONS

Ample evidence has been provided that the response of the very young patient to a pharmacologic agent may be quite different from that of the older child or the adult. Some of the differences between the child and the adult are simply a function of size, and correction of doses by appropriate factors for size, of which body weight is most useful, eliminates these differences. However, it is now clear that it is never justifiable to extrapolate this method of estimating drug dosage for infants in the neonatal period, and that qualitatively different responses are particularly common in the premature infant. The observations discussed indicate the need for a pediatric or neonatal pharmacology, since the responses of the young to pharmacologic agents cannot be predicted until they have been carefully studied. It is possible that similar statements may someday be made about geriatric pharmacology. Currently, new agents are studied in adult animals, and initial human pharmacology, or screening for differences between animal and man, is carried out in the adult. Optimal pediatric therapeutics would result from the careful study of the pharmacology of compounds in newborn and young animals and in infants and children before release for general use. Screening of drugs in very young experimental animals alone would prevent a large part, if not all, of the new examples of iatrogenic toxicity of the sort discussed in this review. Without such controls there will undoubtedly be further examples of toxicity. There is currently no program in the Food and Drug Administration to require proof that a compound is nontoxic to the very young infant before release for general use. Requirements of this sort should be made, but even if this were the case, they would be applicable only to new drugs. Most of the examples of toxicity cited in this review involved agents with which there had been considerable experience and presumably considerable unrecognized toxicity. This constitutes an argument for the extensive use of the controlled clinical trial, especially in nurseries, where it is apparently easy to become committed to the use of routine measures of unproven value. Frequent review of infant and premature mortality rates should bring to light the adverse effects of new regimens. The recognition of altered responsiveness in the very young and the study of the mechanism of such responses may yield information of value to the physiology and pathology of the particular stage of development, as well as to the proper use of the agent under study.

SUMMARY

Evidence has been reviewed for the concept that there is a pharmacology that is peculiar to pediatrics. Adverse responses in

the very young infant to doses which are well tolerated in the more mature have been recognized with increasing frequency in recent years. The newborn and the premature infant are those most frequently affected. The aspects of developmental immaturity responsible for these altered responses account for a variety of mechanisms and it seems likely that future research will bring to light others. It is recommended that suppliers of drugs should be required to establish, before marketing, the presence or absence of differential toxicity in the very young, and it is suggested that further examples of unusual toxicity in this group would be minimized by the use of the controlled clinical trial in the application of established drugs in therapeutic regimens for newborn term and premature infants.

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An outbreak of neonatal deaths among term infants associated with administration of chloramphenicol

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CHLORAMPHENICOL has in the past been considered to be free from serious side effects, other than those associated with bone marrow depression[1-3] or bacterial superinfection.[2-4] The drug was recommended for use in the treatment[5-8] and prophylaxis[6-11] of infections in newborn infants. Recently, however, workers in a number of newborn nurseries have observed acute cardiovascular collapse and increased death rates, especially among premature infants, after administration of this antibiotic.[12-19] In this report, evidence is presented that chloramphenicol was responsible for a sudden outbreak of early neonatal deaths among term infants.

Four unexplained deaths occurred in our newborn nursery during a period of 5 weeks. Sepsis was suspected, but specific evidence of infection was not found. The usual techniques for isolation of possibly ill infants were tightened. Antibiotic therapy was ordered more frequently and in greater magnitude for babies with neonatal respiratory distress or histories of complicated labor or delivery. A vigorous search for an infectious agent was made. In spite of the many precautions, 4 additional term infants and a 2,430 gram infant died from obscure causes during the ensuing 4 weeks. There appeared to be a common pattern to these 9 poorly explained deaths. Postmortem examinations did not reveal the cause of death.

Because all 9 infants had received relatively large doses of chloramphenicol, use of the drug was markedly decreased and was restricted to lower dosage. Thereafter no additional unexplained deaths or complications occurred. An etiological relationship between chloramphenicol and the unexplained deaths was suspected. At that time, however, this drug had been used in

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our own and other newborn nurseries for several years without reported complications. To elucidate further the possible role of chloramphenicol, a survey was undertaken of the administration of antibiotics to newborn infants during the first 3½ years of hospital operation. The data from epidemiologic and microbiologic studies conducted during and shortly after the period of increased neonatal mortality and the results of the retrospective survey as applied to term infants are the substance of this report.

MATERIAL AND METHODS

Maternal and infant medical records were reviewed of all term infants admitted to the newborn nursery of the U.C.L.A. Medical Center who died before 1 week of age or received antibiotic therapy prior to 72 hours of age. The period studied was from July, 1955, through December, 1958. During that period, there were 3,264 infants admitted to the nursery, of whom 7 were born at home or en route to the hospital and the remainder at the Medical Center. Most healthy infants were discharged at 3 to 6 days of age, and no early neonatal deaths are known among those discharged. Late neonatal deaths and the results of chloramphenicol therapy in other infants will be reported elsewhere.[20]

Antibiotic preparations. Antibiotic drugs commercially produced in the United States were administered orally, intramuscularly, or (terminally only) intravenously. The preparations used prior to 72 hours of age for other than terminal care were:

Streptomycin. Streptomycin sulfate in aqueous solution administered intramuscularly.

Penicillin. Aqueous crystalline or procaine penicillin G administered intramuscularly.

Tetracyclines. Usually intramuscular oxytetracycline (Terramycin). Flavored suspensions of oxytetracycline were administered orally to 16 infants and of tetracycline to 4 infants, either exclusively or after several intramuscular injections.

Erythromycin. Usually flavored suspensions given orally. An intramuscular preparation was used for one infant.

Chloramphenicol. Usually the microcrystalline suspension intramuscularly. Lot numbers 224721A and 228773A of Chloromycetin Intramuscular were, so far as could be determined, the only ones used during the outbreak of neonatal deaths. Twenty-one infants received a suspension of chloram-

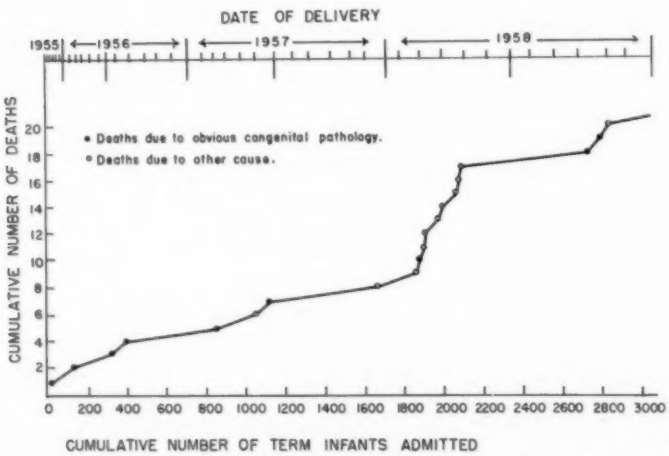
DATE OF DELIVERY
1955
1956
1957
1958
• Deaths due to obvious congenital pathology.
• Deaths due to other cause.
CUMULATIVE NUMBER OF DEATHS
0 2 4 6 8 10 12 14 16 18 20
0 200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600 2800 3000
CUMULATIVE NUMBER OF TERM INFANTS ADMITTED

Fig. 1. Cumulative early neonatal death curve for term infants showing concentration of deaths, particularly poorly explained deaths, between the 1869th and 2,092nd term admissions to the newborn nursery. These infants were delivered between Feb. 22 and April 26, 1958.

Table I. Perinatal death rates for 3½ years and period of outbreak

	Birth weight (grams)	Deliveries between July 5, 1955, and Dec. 31, 1958		Deliveries between Feb. 22 and May 1, 1958	
		Births (No.)	Death rate by 1 week (%)	Births (No.)	Death rate by 1 week (%)
Live births	< 1,001	27	100	3	100
	1,001 to 1,500	28	46	0	
	1,501 to 2,000	38	13	3	0
	2,001 to 2,500	122	7	7	14
	> 2,500	3,049	0.7	240	3.8*
Stillbirths	> 1,000	39	--	2	--
Total births		3,303	3.4	255	5.9†

*P = < .001 for 3.8 per cent or more deaths in any of 12.7 series of 240 consecutive births.
†P = > .05.

phenicol palmitate orally, either alone or in addition to some intramuscular chloramphenicol, and one received crystalline chloramphenicol from capsules orally.

Definitions used.

Term infant. Birth weight over 2,500 grams.

Average dose. This is the total number of milligrams of drug actually administered per kilogram of birth weight divided by the number of days from the first dose until death or until the next scheduled dose after the last dose given.

Mild respiratory distress. Refers to infants with consistent tachypnea to 60 to 90 respirations per minute, but no other signs and no difficulty in initiating respirations.

Moderate respiratory distress. Considered to be present when there were marked retractions, persistent râles, or a respiratory rate consistently over 90 per minute. Included in this group were any infants with small areas of consolidation, granular infiltrate, emphysema, or significant atelectasis in x-rays of the lungs.

Severe distress or depression. Refers to infants with cyanosis, apneic spells, or markedly depressed responses, and includes those with extensive pulmonary collapse or consolidation on x-ray. Included are any infants strongly suspected of sepsis at the time of evaluation.

Microbiologic studies. Bacteriologic cultures were performed in the hospital clinical laboratories whenever suspicion of infection arose. In addition, between April 20 and May 6, 1958, nasopharyngeal and throat cultures were obtained from all of the 57 infants admitted to the newborn nursery.* Specimens were taken from 52 infants within a few hours of birth, from all 57 at 1 and 2 days of age, and from 18 at 4 days of age.

Virus isolation was attempted from autopsy material from 5 infants and from the stool of one infant who survived similar symptoms.† All specimens were inoculated into HeLa cells and human amnion cells (FL line), and 5 were followed through several passages. In addition, 8 preparations were injected into newborn mice, 2 were given intranasally to adult mice, and 3 were inoculated into monkey kidney and one into eggs.

DESCRIPTION OF THE OUTBREAK

The accumulation of early neonatal deaths in term infants during the months of March and April, 1958, is illustrated in Fig. 1. All but one of these infants died of obscure causes. In contrast, 8 of the 11 deaths outside this period were easily explained on

*These studies were performed under Dr. Ruth Boak of the Department of Infectious Diseases, U.C.L.A. Medical Center.

†Virus studies were performed by Dr. Pamela Byatt in the Department of Clinical Laboratories, U.C.L.A. Medical Center. Additional specimens from 2 infants were examined independently by Dr. Ruth Boak.

Table II. Infants who died of poorly explained causes, Feb. 22 to May 1, 1958

					Maternal			*Complications*			*Drugs*	
Case	*Birth date (1958)*	*Sex*	*Race*	*Birth weight (grams)*	*Parity*	*Rupture of amniotic sac (hours)*	*Labor (hours)*	*Mode of delivery*	*Manifestations (age at onset in hours)*	*Results of therapy (age in hours)*	*Drug*	*R*
1	2/22	M	W	3,100	1	0	2	Spontaneous, vertex	Omphalitis (39) Lethargy (141) Shock, congestive heart failure (148)	Improved Died (157)	Chl Chl Chl	
2	3/7	F	N	3,840	0	13	24	Spontaneous, vertex	Amnionitis Moderate respiratory distress (2) Hypothermia (16) Seizures, lethargy (18)	 Worse (16) Improved (18) Died (44)	Chl Pen	
3	3/8	M	N	2,880	0	3	23	Spontaneous, vertex	Lethargy, atalectasis (0) Edema, cardiomegaly (19) Bleeding tendancy (28) Shock (48)	Improved (1) Worse Worse Died (65)	Chl Chl Dig	
4	3/28	M	W	3,570	0	28	29	Cesarean section, vertex	Moderate respiratory distress (12) Lethargy (77) Shock (83)	Improved Died (92)	OTet Chl Chl	
5	4/2	M	W	4,120	0	18	7	Cesarean section, breech	Mild respiratory distress (0) Moderate respiratory distress (18) Fever (32) Shock (99)	Improved (2) Improved (72) Improved (40) Died (101)	Chl Chl Ery	
6	4/13	F	W	2,430	2	4	4	Spontaneous, vertex	Moderate respiratory distress (8) Lethargy (66) Shock (74)	Improved (56) Died (77)	Chl Ery	
7	4/21	M	W	4,100	0	12	13	Cesarean section, vertex	Mild respiratory distress (12) Circumcision (88) Shock, congestive heart failure (88½)	Improved (65) Uncomplicated Died (100)	Chl Ery	
8	4/24	F	N	2,800	3	30	2	Spontaneous, vertex	Lethargy (116) Shock, congestive heart failure (117)	 Died (132)	Chl Ery	
9	4/26	M	N	2,740	0	50	19	Spontaneous, vertex	Mild postmaturity Circumcision (106) Lethargy (110) Shock, congestive heart failure (111)	 Uncomplicated Died (119)	Chl Ery	

Drugs started before terminal episode*						Microbiologic studies			
		Age in hours		Doses					
Drug	Route	First dose	Last dose	Daily (mg./Kg./day)	Total (mg./Kg.)	Before antibiotics	After antibiotics	Post mortem	Possibly significant autopsy findings
Chl	PO	58	90	145	241	Urine, nonpathogens		Blood, negative	Slight pericholangiolitis
Chl	IM	108	148	145	289				Mod. pulm. hem.
Chl	IV	151	157		19	Blood, negative			Small interatrial septal defect
Chl	IM	3	40	117	236		Cerebrospinal fluid, negative	Blood, negative	Slight interstitial pneumonia
Pen	IM	20	36	26	26				Mod. pulm. hem.
Chl	IM	9	24	188	143		Blood, negative	Blood, negative	Anasarca
Chl	IM	29	59	139	208				Moderate pulmonary hemorrhage
Dig	IM	29			0.04				
OTet	IM	2	78	56	196		Urine, throat, nasopharynx, stool, nonpathogens	Lung, flavobacterium and pseudomonas	Severe pulm. hem.
Chl	IM	22	78	168	450				Necrosis at injection site
Chl	IV	87	92		11				Cerebral edema
Chl	IM	1	97	109	473		Urine, throat, nonpathogens	Blood, negative	Severe pulmonary hemorrhage
Chl	IV	98	101		21			Blood, lung, negative	Severe fatty liver
Ery	PO	25	97	55	182		Nasopharynx, stool, blood, negative	Stool, virus studies negative	
Chl	IM	14	70	154	411	Nasopharynx, negative	Nasopharynx, stool, blood, negative	Blood, *E. coli* (19 hr. post mortem)	Mod. pulm. hem.
Ery	PO	15	70	62	165				Slight bronchopneumonia
								Brain, lung, bronchus, virus studies negative	Slight hyaline membrane
									Mediastinal lymphadenopathy
Chl	IM	13	96	138	511	Nasopharynx, throat, negative	Nasopharynx (×2), throat, negative	Blood, negative	Severe pulmonary hemorrhage
Ery	PO	13	88	73	238		Throat, nonpathogens	Stool, virus studies negative	Aspiration amniotic fluid
Chl	IM	6	100	134	580	Amniotic fluid, nonpathogens	Nasopharynx (×2), throat, (×2), negative	Blood, negative	Severe pulmonary hemorrhage
Ery	PO	6	100	54	232	Nasopharynx, throat, negative		Blood, stool, lung (×2), liver, trachea, colon, virus studies, negative	Renal hemorrhage
Chl	IM	5	93	142	569	Amniotic fluid, negative	Nasopharynx (×2), throat, (×2), negative	Blood, negative	No autopsy
Ery	PO	5	93	49	197	Nasopharynx, throat, negative		Stool, nonpathogens	
								Blood, stool (×2), virus studies neg.	

*Antibiotics and other drugs in addition to those listed were given terminally (after the onset of shock) to all but Cases 2 and 3. Chl—chloramphenicol, Dig—digoxin, Ery—erythromycin, Pen—penicillin, OTet—oxytetracycline, IM—intramuscularly, IV—intravenously, PO—orally.

the basis of obvious congenital disease.* A "period of outbreak" has been designated from the birth of the first infant who died of poorly explained causes (Feb. 22, 1958) to the death of the last infant in the group (May 1, 1958). Four per cent of the 240 term infants delivered during these 68 days died before the age of 1 week. Prior to and after the outbreak, the early neonatal death rate for term infants was 0.4 per cent. As shown in Table I, the significant increase in deaths during the outbreak was confined to mature infants.

Deaths during the outbreak. There were 13 early neonatal deaths among infants admitted to the nursery between February 22 and May 1. Three infants were immature. Of the 10 deaths among term or near-term infants, only one was adequately explained by postmortem examination; it was due to a massive intracranial hemorrhage with death at 20 minutes of age. Clinical data on the other 9 infants are given in Table II. Three were born by cesarean section after difficult labor and 2 others after prolonged labors. Six of the infants had definite respiratory trouble or depression shortly after birth, but in only 2 cases (2 and 3) was there considered to be significant threat to life before the terminal episode. One baby (Case 1) developed mild omphalitis on the second day of life from which no pathogenic organisms were isolated.

Prior to the onset of the terminal episode, all these infants were treated with chloramphenicol for prophylaxis or treatment of suspected infection. Other drugs administered to some of the infants are listed in Table II. Three of the babies were born more than 24 hours after rupture of the amniotic membranes. Their mothers received oxytetracycline for 5 to 14 hours before delivery. Two of these infants (Cases 8 and 9) were completely healthy at delivery and remained so until 4½ days of age. Five other babies (Nos. 1, 4, 5, 6, and 7) showed definite improvement in their primary condition to the point that they were returned to the mother and breast feedings, were transferred to open bassinettes, or were being prepared for discharge. In 2 of these cases (6 and 7) an impression of pallor or grayish appearance was occasionally recorded, although the infants appeared vigorous. After definite improvement or periods of complete health there was, 2 to 4 days after the first administration of antibiotic, a rapid onset of listlessness and difficult feeding. Within a few minutes to hours all of the infants became cold, clammy, and flaccid, with ashen color, blotchy skin, feeble pulse, indeterminable blood pressure, and little or no response to stimulation. Four infants had enlarged livers and enlarged hearts, which were not noted on previous examinations. Therapy during the terminal episodes included additional intravenous antibiotics, hydrocortisone, epinephrine, methoxamine, digoxin, lanatoside C, and whole blood. The infants died within 2 to 17 hours of the onset of shock. In 3 cases, diffuse râles were noted just prior to death.

Death occurred after 44 hours of age in all 9 of these cases and after 72 hours in 7 of them. By contrast, only 2 of the 10 early neonatal deaths of term infants outside of the outbreak period took place after 44 hours of age. In addition, of 20 term infants delivered by elective cesarean section after a trial of labor during the 3½ years of study, only one died in addition to Cases 4, 5, and 7 in Table II.

Pathology. Eight of the 9 infants were examined post mortem.* Pulmonary hemorrhage was present in all.[20] In several cases, this was considered sufficient to have been a cause of death by suffocation or exsanguination. In only 2 cases (1 and 6) was there significant suggestion of infection and this was not adequate to explain death, being restricted to mild lymphadenitis in one and pericholangiolitis in the other. The presence of congestive heart failure was confirmed in the infants in whom it was suspected clin-

*Congenital heart disease (2), meningitis (2), bronchopneumonia (2), myelomeningocele or hydrops fetalis. Only one term infant is known to have died between 1 week and 1 month of age. She had an encephalocele.

*The slides of all were reviewed by Dr. Harrison Latta of the Department of Pathology, U.C.L.A. Medical Center.

Table III. Results of bacterial cultures from term and premature infants during outbreak period

Organism	Site cultured prior to chemotherapy			
	Nasopharynx and/or throat*	Skin or umbilicus	Blood	Placenta or amniotic fluid
Sterile	8 (4 died)	1	5 (1 died)	2 (1 died)
Nonpathogens only†	29	2 (1 died)	1	1 (1 died)
Staphylococcus aureus	1	2		
Escherichia coli	1	1		1
Other possible pathogens‡	3			

*All 37 infants delivered between April 20 and May 1 had two or more nasopharyngeal and throat cultures.
†*Staphylococcus epidermidis*, alpha hemolytic streptococcus, *Neisseria catarrhalis*.
‡*Proteus mirabilis*, beta hemolytic streptococcus, *Hemophilus influenzae*.

ically. There was evidence of some aspiration of amniotic debris in all cases, but this was thought significant in only one case (No. 7) in which it was considered insufficient to cause death. Several infants had fatty infiltration of the liver and 3 had mild adrenal tubule formation consistent with circulatory collapse.[21] These pathologic observations were not significantly different from those found in other newborn infants who die from more evident causes.

There was extensive necrosis of the muscle and fat at the site of chloramphenicol injections in one infant.

Other morbidity during period of outbreak. All of the infants who died spent some time in either the premature or "suspect" nursery, or both. Thus, the possibility of cross-infection by an unknown organism was present. During the same period, however, in addition to the babies who died, 7 premature infants, 3 of them with birth weights under 2,000 grams, and 24 term infants were admitted to the same segregated nurseries for observation periods of one to 25 days. Illness among these infants was limited almost entirely to mild respiratory distress, usually after difficult deliveries. One term infant developed significant complications. He was segregated because of moderate neonatal respiratory distress, received chloramphenicol and erythromycin, improved, and subsequently developed depression, seizures, spasticity, edema, and oliguria. This baby was considered at the time to be suffering from an illness similar to that of those who died, possibly viral encephalitis, but the cerebrospinal fluid contained no cells. After one week he began to improve gradually and no diagnosis was made.[20]

In addition, there were 2 one-week periods of suspected staphylococcal infection involving, at most, a total of 8 infants with minimal "omphalitis" or "pustules." *Staphylococcus aureus* was isolated from 2 of the 6 infants from whom cultures were made. No other pathogens were found. Only one of these babies developed any systemic signs or symptoms (Case 1).

Microbiologic studies (Tables II and III). During the period of outbreak, the nasopharynx and/or throat of 42 infants were cultured prior to any antibiotic therapy, in most cases several times. *Staphylococcus aureus* was obtained from only one infant. Another infant who received a single dose of oxytetracycline because of birth out of asepsis had sterile cultures at birth, but a

Table IV. Effect of antibiotic therapy on early neonatal fatality rates in term infants treated before 72 hours of age

Antibiotic agents administered	Number of infants who received antibiotic		
	At least 24 hours of therapy		Died before 24 hours of therapy
	Lived	Died	
Penicillin	40	1	3
Streptomycin	36	0	3
Tetracyclines	42	1	1
Erythromycin	7	5	0
Chloramphenicol	43	10	2
Total*	124	10	6

*Some infants received 2 to 4 antibiotics.

Table V. Reasons for antibiotic therapy in term infants who received at least 24 hours of therapy beginning within 72 hours of birth

*Major reason for antimicrobial therapy**	*Received chloramphenicol*		*Did not receive chloramphenicol*	
	Infants	*Deaths*	*Infants*	*Deaths*
Severe distress or depression	5	1	2	0
Moderate respiratory distress	7	3	8	0
Mild respiratory distress	3	2	2	0
Omphalitis, mild	5	1	0	0
Amnionitis	1	0	1	0
Premature rupture of amniotic membranes (> 18 hours)	19	2	36	0
Endotracheal intubation at birth	4	0	8	0
Exchange transfusion	1	0	8	0
Birth out of asepsis	5	0	13	0
Others	4†	1	2‡	0
Total	54	10	80	0

*When there was more than one reason for antibiotic therapy, the infant is included under the reason highest on the list.

†Melena, postmaturity emesis, anemia.

‡Jaundice, thrombocytopenia.

single colony of *Staphylococcus aureus* grew from one of his six subsequent nasopharyngeal and throat cultures. There were no clinical manifestations in these infants. The incidence of staphylococcal infection among infants in the nursery was lower during a 10 day survey at the last of the outbreak period than during the week following the outbreak or other periods in which the nursery was surveyed.

All attempts at viral isolation from autopsy material from the last 5 infants who died and the infant with encephalitic symptoms were unsuccessful.

RESULTS OF RETROSPECTIVE STUDY

The data on antibiotic therapy of infants born in the hospital between 1955 and 1958 were organized on a time scale. The resulting patterns of changing chemotherapy are shown in Fig. 2. It was found that the antibiotics of preference, as well as the incidence of antibiotic therapy, varied with the medical staff rotating through nursery duty every one to three months, as well as with the trends of the time.

The peak use of antibiotics was between July and December, 1957, but this was not associated with increase in infection rate or death rate. Chloramphenicol was extensively used during that period, but the doses were usually below the median dose (75 mg. per kilogram per day)* used in our nursery. The use of higher doses of chloramphenicol (over 113 mg. per kilogram per day)* was confined almost entirely to the period of increased neonatal mortality. In contrast, dosage for all other antibiotics was found to be related more to the severity of the illness than to the month of administration. An average of 135 mg. per kilogram per day of chloramphenicol was administered during the outbreak period, compared with 90 mg. for the entire 3½ years, 73 mg. prior to the outbreak, and 65 mg. after the outbreak.

Relation of antibiotic therapy to neonatal mortality. Table IV gives the distribution of antibiotic therapy for the 134 term infants who received therapy for at least 24 hours beginning before the age of 72 hours. The entire 3½ years of study are included. Only 10 of these infants died, and all 10 received over 108 mg. per kilogram per day of chloramphenicol either alone or with one or several other antibiotics. For none of these infants was an adequate pathologic explanation for death found,† and all but 2

*The median of the average doses received by each infant is used as a standard for comparison of therapy with the various antibiotics. High doses are then considered to be those which are more than 1.5 times the median dose. The median 24 hour doses per kilogram were: penicillin, 38,000 units; streptomycin, 38 mg.; the tetracyclines, 50 mg.; erythromycin, 60 mg.; and chloramphenicol, 75 mg.

†The only other infant who died without adequate explanation during the entire 3½ year period, the last one in Fig. 1, was found dead in a crib at 50 hours of age. A coroner's postmortem diagnosis was "bronchiolitis." Slides were not available for review.

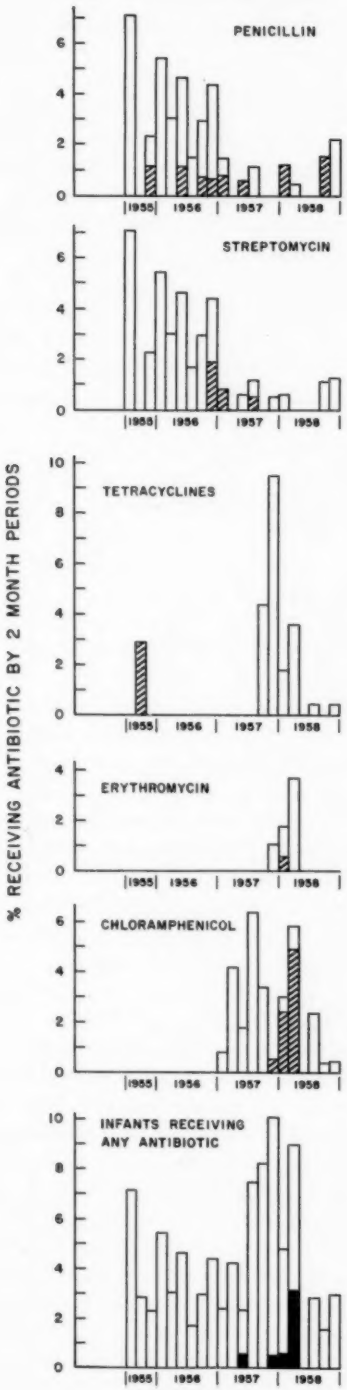

Fig. 2. Patterns of antibiotic therapy in the newborn nursery. White columns, per cent of all infants admitted in each 2-month period who received the antibiotic for at least 24 hours beginning before the age of 72 hours. Solid black columns, per cent who died after at least 24 hours of antibiotic therapy. (All of these infants received chloramphenicol in doses of over 108 mg. per kilogram per day.) Diagonal lines, per cent who received more than 1.5 times the median dose used in the nursery.*

*See footnote under Results of Retrospective Study.

were born during the period of outbreak. One of the others had a clinical course almost identical with that of Case 7 in Table II.

Fig. 3 shows the scatter of chloramphenicol doses used in the nursery. Twelve infants received more than 110 mg. per kilogram per day of chloramphenicol, and a cumulative dose over several days of 400 mg. per kilogram or more, with a 67 per cent fatality rate. The infant who survived unexplained central nervous system complications was also in this group, giving a delayed morbidity rate of 75 per cent.

The distribution of antibiotic therapy shown in Table IV suggests association of increased mortality with administration of erythromycin. However, erythromycin was used almost exclusiveiy with chloramphenicol, and no correlation could be demonstrated between mortality and erythromycin dosage. The only 2 infants who received erythromycin without simultaneous administration of chloramphenicol developed no complications.

Reasons for antibiotic therapy. In 3½ years 6 term infants were so ill at the time of initial antibiotic therapy that they survived only one dose. Only 2 of these received chloramphenicol (Table IV). This suggests that chloramphenicol was not the principal drug used for severely ill infants. To test further the comparability of the chloramphenicol-treated infants with those who did not receive the drug, the results of therapy in the two groups were tabulated according to the reasons for therapy (Table V). There was little correlation of the

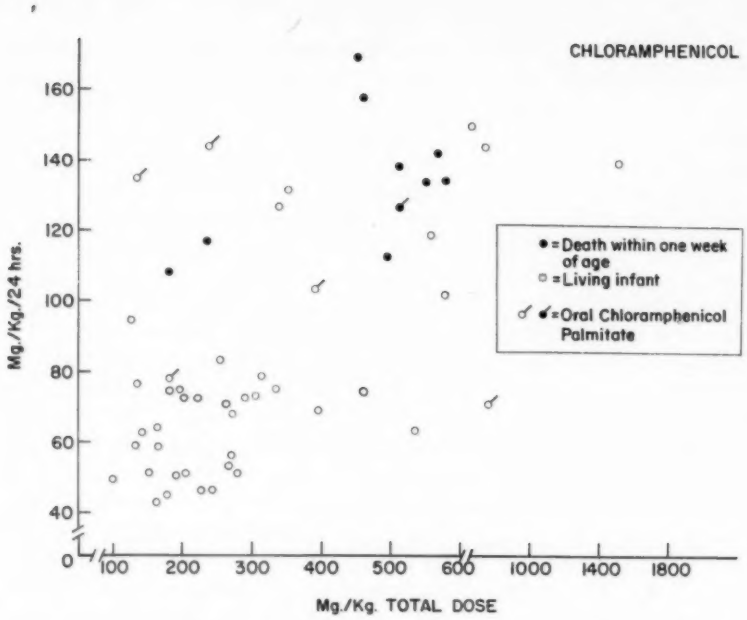

Fig. 3. Scattergram of total and daily doses of chloramphenicol showing all term infants who received the drug for over 24 hours starting within 3 days of age. More than half of the chloramphenicol was administered as the intramuscular microcrystalline suspension unless otherwise indicated.

death rate with the reasons for antibiotic therapy among infants who lived at least 24 hours after the beginning of therapy. The death rate was actually higher among the infants treated for mild illness than among those treated for more severe illness.

DISCUSSION

The concentration of early neonatal deaths in term and near-term infants during March and April, 1958, was an unusual occurrence of sufficient statistical significance to warrant a search for a causative agent. The presence of such a common etiology was substantiated by discovery of marked similarities among 9 of the 10 infants who died:

1. All received early antibiotic therapy for prevention or treatment of suspected infection.

2. The clinical courses were distinctive, being marked by improvement in initial symptoms or by lack of symptoms followed by sudden onset of vascular collapse at 2 to 5 days of age.

3. There was lack of confirmation of infection despite extensive search for infectious agents.

4. Autopsies did not reveal a cause of death, unusual among term infants in our nursery.

A search for etiological factors in an outbreak of disease among newborn infants must not be limited to infectious agents. Obstetric practice, infant care techniques, nursery environment, preparation of feedings, and drug therapy of both mothers and infants must also be examined. In this study, the only unique common factor discovered after such a survey was the administration of chloramphenicol in doses over 113 mg. per kilogram per day for 41 hours or longer. When first discovered, this association was thought to be fortuitous, caused by the fact that chloramphenicol was the drug preferred for use for seriously ill babies by many physicians. On review, however, it appeared that the infants listed in Table II were no more ill at the beginning of chemotherapy

than others who received antibiotics during the same or other periods without complications.

A retrospective survey of antibiotic therapy in the newborn nursery established that high doses of chloramphenicol were not selectively used for seriously ill patients, yet were associated with an exceedingly high mortality rate among term infants. Forty term infants received chloramphenicol in doses of 42 to 107 mg. per kilogram per day and 78 were given other antibiotics without a death.

These data strongly suggest a causal relationship between chloramphenicol administration in high dose and at least 8 deaths of term and near-term infants (Cases 1, 4, 5, 6, 7, 8, and 9, and an additional one in December, 1958). Such a relationship is suspected in the deaths of 3 other term infants who possibly had sufficient primary illness to have caused death, but had atypical clinical courses and minimal pathologic findings (Cases 2 and 3, and another in May, 1957).

Chloramphenicol toxicity in the newborn. Acute onset of a grayish appearance and signs of vascular shock were the major manifestations among our infants, as well as others whose deaths have been attributed to administration of chloramphenicol.[13-19] Four of our infants had evidence of congestive heart failure. Sutherland[13] reported 2 cases with dilated hearts and one with congestion of the liver, and Van Gelder[14] mentioned 2 infants who developed sudden nonfatal congestive heart failure. Neurological signs in Case 2 and in an infant who recovered from acute encephalitic symptoms during the outbreak may have been related to chloramphenicol administration. It is likely that the manifestations of chloramphenicol intoxication in the newborn are protean, involving most organs occasionally.[20] The mechanism of action is unknown, but it appears that the very high incidence of toxic reactions in newborn infants is related at least in part to impaired glucuronide conjugation (possibly at a different site than that of bilirubin conjugation) and impaired renal excretion, leading to retention of the free drug and blood levels above 100 μg per milliliter.[17-19] Accumulation of chloramphenicol can occur after either oral or intramuscular administration. The toxic dose appears to be in the same range for susceptible premature[15, 18] and term infants, though it may be somewhat lower for severely ill infants.[20] Prolonged absorption of the intramuscularly administered microcrystalline suspension has also been demonstrated.[19] This accounts for the delayed appearance of shock in our Cases 8 and 9 and in that of Sutherland and coworkers.[17]

Between 1951 and 1959, the usual dose of chloramphenicol recommended for intramuscular use in "infants and children" was 100 to 150 mg. per kilogram per day.[22-25] This dose was also used for newborn and premature infants.[9] Some workers suggested schedules which provided still higher doses when applied to newborn infants.[3, 26-31] Specific dose proposals for use with intramuscular chloramphenicol in newborn infants were between 110 and 264 mg. per kilogram per day.[6-8, 31] It is thus evident that most of the previously recommended dose schedules were potentially injurious to newborn infants, especially if continued for more than 3 days.* There appear to be two reasons for the delayed discovery of this fact:

1. In spite of multiple recommendations, chloramphenicol probably was not used much for newborn infants until 1957. The major earlier reports, we have found, involved short-term therapy without evident toxicity.[31, 32] A number of workers[33] gave 150 to 165 mg. per kilogram per day of chloramphenicol to infants with diarrhea under 1 month of age. Blood levels as high as 120 μg per milliliter were reported,[34] and it is conceivable that toxic deaths in the

*No toxic manifestations have been reported on the dose schedule currently recommended by Parke, Davis & Company, 50 mg. per kilogram per day for term newborn infants and 25 mg. per kilogram per day for premature infants; however, some data[19] indicate that lower doses would be adequate to maintain therapeutic levels after the first 24 hours.

newborn period were missed because of lack of age-specific fatality rates.

2. It is difficult to distinguish the symptoms associated with chloramphenicol overdosage from those due to infective toxemia of the newborn.[35] Only when relatively healthy infants received the drug could the toxic manifestations be clearly distinguished. Thus, as early as 1951, 3 cases of shock, anuria, acidosis, and death were described after administration of 2 Gm. of chloramphenicol in 24 hours to 6 newborn infants.[36] The significance of this observation was not fully recognized because of the similarity of the illness of these infants to that of 13 others who did not receive chloramphenicol for the same infection, *Salmonella oranienburg* diarrhea. It is impossible even now to be sure that these and other apparently chloramphenicol-induced deaths were not caused by sudden release of bacterial endotoxins or by sensitization of the infant to these or viral toxins.

Circulatory collapse in older individuals receiving chloramphenicol. The duration of the danger period for chloramphenicol overdosage is not yet established. Blood level studies[19] indicate that some chloramphenicol retention persists through 10 to 16 days of age. Van Gelder[14] mentions an infant who developed acute collapse associated with chloramphenicol administration at 25 days of age. Experience in our hospital indicates that infants over 3 weeks of age have usually tolerated doses up to 200 mg. per kilogram per day, but it is possible that a few severely ill or dehydrated infants have been further weakened by administration of chloramphenicol.[20] Doses as high as 480 mg. per kilogram per day have been administered to older infants without toxicity.[37] In contrast, however, acute circulatory collapse was observed in 1954[38] in infants treated for 3 to 5 days with only 50 mg. per kilogram per day of chloramphenicol, leading to the tentative conclusion that "marasmic children with gastroenteritis tolerated chloramphenicol badly."

Acute circulatory collapse after treatment of adults and children with moderate or high doses of chloramphenicol has been reported many times,[3, 13] but with few exceptions[39] this has been associated with therapy of Salmonella infections. The occurrence of shock has usually been attributed to rapid release of endotoxin associated with death of the typhoid bacillus, but there is reason to doubt this explanation.[40] The possibility that these isolated occurrences may also be due to abnormal retention of chloramphenicol or its metabolic products is under investigation.

Outbreaks of chloramphenicol intoxication. Perhaps other previously unexplained outbreaks in newborn nurseries will be found on review to have been due to administration of chloramphenicol. In our nursery, the dose of chloramphenicol and the incidence of its use were actually increased as the gravity of the outbreak became evident. Only after careful review and reconsideration was the relationship between death and drug administration suspected. In the outbreak described by Van Gelder and co-workers,[41] the association of chloramphenicol with at least some of the deaths did not become evident until after neonatal chloramphenicol intoxication was announced by Parke, Davis & Company.[14] When other major illness is present, it is difficult to detect outbreaks of drug-induced morbidity or mortality, but a high level of suspicion must be maintained.

SUMMARY

The evidence presented strongly suggests that administration of chloramphenicol in previously recommended doses was responsible for an outbreak of early neonatal deaths in a newborn nursery. A death rate of 67 per cent is reported for 12 term infants who received over 110 mg. per kilogram per day and a cumulative dose over several days of 400 mg. per kilogram or more. Death occurred at 2 to 5 days of age after the sudden appearance of vascular collapse. Similar deaths have been reported in connection with chloramphenicol administration, particularly of premature infants, but possibly of certain older children and adults.

The striking similarity between this outbreak of deaths, thought to be due to drug administration, and any outbreak of infectious disease emphasizes the need for broad epidemiologic investigation of any unusual occurrence in a newborn nursery.

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Severe infections in children due to rare gram-negative bacilli (Mima polymorpha and Bacillus anitratum)

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IN 1939 De Bord[1] described a group of gram-negative pleomorphic microorganisms which had previously been observed in cases of meningitis and of "drug-resistant gonorrhea." The designation, tribe Mimeae, assigned to them in 1942[2] is based on their ability to imitate other bacteria, especially the Neisseria. *Mima polymorpha,* for instance, owes its name to its ability to assume many forms and to mimic other organisms; *Bacillus anitratum* is another member with similar characteristics.

The purpose of this communication is to emphasize that these unusual infections occur in variable forms which can be confused with more common clinical entities, and that the organisms are quite variable in their susceptibility to available antimicrobial agents. Hence treatment should be based on isolation of the organism and determination of its in vitro susceptibilities to sulfonamides and antibiotics.

During the years 1956 to 1959, 7 severe infections by members of the tribe Mimeae were diagnosed and treated in the Pediatric Service of the San Juan City Hospital. The clinical and laboratory findings of these patients are described.

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CASE REPORTS

Case 1 (T. G. N. No. 1). This premature infant, one of twins, birth weight 4 pounds, 9 ounces, was apparently well until the fourth day of life when she developed slight cyanosis, respiratory difficulty, and weakness. She vomited frequently; thrush appeared on the sixth day of life. She was afebrile throughout the course of her illness except for a temperature of 101° F. on the sixteenth day of life, 2 days after her transfer to the Pediatric Service. When admitted to this Service, she was visibly dehydrated, irritable, and in poor condition. The anterior fontanel was a little tense. There was no nuchal rigidity. There were coarse râles over the left base posteriorly and at the axillary line, with diminished breath sounds. Examination of the spinal fluid revealed 10,000 white blood cells per cubic millimeter, 97 per cent of which were

neutrophils, 466 mg. of protein per 100 c.c., and 12.6 mg. of glucose per 100 c.c. *M. polymorpha* was cultured from the spinal fluid and the peripheral blood. The peripheral white blood cell count was 19,250 per cubic millimeter; polymorphonuclear leukocytes 82; lymphocytes 15; monocytes 3 per cent on admission and 43,500 5 days later.

The patient was treated with intravenous fluids, blood transfusions, other supportive measures, and a combination of sulfadiazine (0.2 per cent per kilogram, by clysis), chloramphenicol (50 mg. per kilogram), and streptomycin (50 mg. per kilogram), intramuscularly. In vitro sensitivity testing demonstrated sensitivity of the organism to chloramphenicol and to streptomycin.

The baby seemed to improve for a while and the lungs cleared. However, soon afterward, she was again weak and apathetic. One week after her transfer to the Pediatric Service the fontanel was still tense. The next day she was found gasping; rhonchi were heard over the entire chest; she died rather suddenly. She was then 22 days of age.

The postmortem diagnoses were leptomeningitis, atelectasis, bronchopneumonia, and prematurity.

Case 2 (M. G. N. No. 2). The twin sister of the previous patient weighed 4 pounds, 6 ounces at birth. She developed symptoms one day after her sister, when she was 5 days old. She had fever, intermittently and her condition deteriorated progressively, she had thrush, jaundice, purulent drainage from both ears, and, terminally, parotitis. Only at the end did she have inconstant pulmonary râles. There were no signs of meningitis. She died at the age of 14 days. Cultures of the blood and of the purulent discharge from the ears revealed *M. polymorpha*. Antibiotic therapy included oxytetracycline (50 mg. per kilogram orally), chloramphenicol (50 mg. per kilogram intramuscularly), and polymyxin B (2.5 mg. per kilogram intramuscularly). The postmortem diagnoses were pneumonitis with venous thrombi and endothelial lesions in the venules, bilateral suppurative otitis media, parotitis, and prematurity.

Case 3 (A. R.). At the age of 5 days this child was noticed to be icteric but had no anemia and a negative Coombs test. During the next 2 days, the jaundice seemed to be clearing, and he was in good condition. The following day at noon he became irritable and restless and developed fever. He cried all afternoon and then was brought to the hospital, where on admission he had a temperature of 103° F. and a tense bulging fontanel. No rigidity of neck, jaundice, enlargement of the spleen, or other significant physical finding was present.

There were 400 cells in the spinal fluid (88 per cent polymorphonuclear leukocytes), 18 mg. of glucose, and 234 mg. of protein. Gram-negative organisms were seen in the smears which were identified as *M. polymorpha* in the culture. The blood culture contained bacteria presumed to be contaminants. Normal flora was obtained from the vaginal culture of the mother; there was no growth of *M. polymorpha*. The white blood cell count on the patient was 24,000 per cubic millimeter with 86 per cent polymorphonuclear leukocytes.

The patient was started on chloramphenicol (100 mg. per kilogram daily intramuscularly), sulfadiazine (0.2 Gm. per kilogram daily), and penicillin (1,000,000 units intramuscularly every 2 hours). In

Fig. 1. Case 7. Bone lesion of upper metaphysis, left femur.

Fig. 2. Case 7. Osteomyelitic lesion of distal metaphysis, left radius.

accord with sensitivity tests, the therapy was shifted later to courses of streptomycin, Terramycin, tetracycline, and erythromycin, singly or in combinations. Three courses of chloramphenicol were tried. Because of a low serum gamma-globulin level, blood transfusions and intramuscular gamma globulin were administered.

Therapy was of no avail. Although the patient remained afebrile most of the time, he gradually grew worse, had frequent episodes of convulsions, and, finally, opisthotonus and mild hydrocephalus. Repeated spinal taps throughout the 7 weeks' course and 2 ventricular taps revealed the persistent presence of *M. polymorpha* and the usual changes seen in uncontrolled purulent meningitis. He died 52 days after admission.

The postmortem diagnoses were purulent meningitis, severe cerebral edema with increased intracranial pressure, severe dehydration, patent foramen ovale, and decrease in thickness and pallor of the adrenal cortex.

Case 4 (M. S. F.). This 5-month-old female infant developed a white nasal discharge and dry cough 4 days prior to admission. One day before admission she refused feedings and developed high fever, projectile vomiting, restlessness, and convulsions.

On physical examination the baby was found to have a temperature of 103° F., and was irritable, with generalized spasticity. The fontanel was tense but not bulging; the neck was moderately rigid, and the Kernig and Brudzinski tests were positive. There were nasal discharge and injection of the pharynx and eardrums. The chest was clear; the spleen was not palpable. Other systems were normal.

Examination of the spinal fluid revealed 3,380 white blood cells per cubic millimeter with 90 per cent neutrophils, 220 mg. of protein per 100 c.c., and 16 mg. of glucose per 100 c.c. Gram-negative pleomorphic organisms were seen in smears of the spinal fluid, and *M. Polymorpha* was isolated on culture. The organisms were sensitive in vitro to sulfonamides and to a variety of antibiotics including chloramphenicol. Therapy consisted of intravenous fluids, transfusions of blood, gamma globulin, and various antibiotics.

The clinical course was stormy with high fever and repeated convulsions during the first few days. The spinal fluid became negative slowly, except for some pleocytosis. Three more febrile episodes occurred in about 10 days; there were no abnormal spinal fluid findings, and subdural taps were negative. One of the last 2 episodes was associated with diarrhea (negative stool culture) and the other with a subcutaneous abscess. The infant gradually improved and recovered completely after hospitalization for 2 months.

Table I

Case	*Disease*	*Age at onset*	*Outcome*	*Organism*
1. T. G. N.[1]	Meningitis	4 days	Died	*M. polymorpha*
2. M. G. N.[2]	Sepsis	5 days	Died	*M. polymorpha*
3. A. R.	Meningitis	8 days	Died	*M. polymorpha*
4. M. S. F.	Meningitis	5 months	Recovered	*M. polymorpha*
5. M. H. M.	Sepsis	2 years	Recovered	*M. polymorpha*
6. C. A. C.	Sepsis	15 months	Recovered	*B. anitratum*
7. J. A. R. T.	Sepsis, osteomyelitis	6 months	Recovered	*B. anitratum*

Case 5 (M. H. M.). This patient was a 2-year-old female infant with a history of 2 previous episodes of asthma. Overnight, before admission to the hospital, she developed fever, cough, and severe respiratory distress with marked tachypnea and cyanosis. On examination of the chest wheezing, scattered coarse râles were noted; tachycardia was prominent. Soon after admission she had a convulsion, became unconscious, and remained in critical condition for several days. There were no meningeal signs, and examination of the spinal fluid was negative. Culture of the blood revealed *M. polymorpha,* sensitive to broad-spectrum antibiotics and resistant to penicillin. The child remained seriously ill for several days. It was the clinical impression that she had bilateral bronchopneumonia, associated with the *M. polymorpha* septicemia. Cardiac failure occurred during the course of the illness, and she received Cedilanid. She recovered gradually under treatment consisting of penicillin at first and then of polymixin B and chloramphenicol. Her illness was complicated by roentgen evidence of tuberculosis (small, persistent pulmonary infiltrate and increased hilar markings); the tuberculin skin test (PPD) was positive. It was deemed that the tuberculosis was not active at the time, but she left the hospital under chemotherapy for tuberculosis.

Case 6 (C. A. C.). This 15-month-old female infant had a history of vomiting and diarrhea, watery, foul, nonbloody, for 3 days. Besides the signs of dehydration, pallor and a temperature of 106° F. were noted on the initial examination, with no evidence of a localized infection. Culture of the blood was positive for *B. anitratum.* The organism was shown to be sensitive in vitro to broad-spectrum antibiotics and resistant to penicillin. There was marked leukocytosis with 33,450 white blood cells per milliliter of which 70 per cent were neutrophils. Therapy consisted of intravenous fluids, oral neomycin with kaolin and pectin, and tetracycline, 50 mg. per kilogram per day. The child responded well and was afebrile within 48 hours. Diarrhea ceased 2 days later.

Case 7 (J. A. R. T.). This 6-month-old

Table II. Bacteriologic characteristics of the tribe Mimeae*

	Mima	*Herellea*	*Colloides*
Carbohydrates	Not fermented	Acid Glucose Xylose Lactose 10%	Acid and gas Glucose Lactose Maltose
Imvac	Negative	Citrate positive	Methyl red positive Indole positive Citrate positive
Nitrates	Not reduced	Not reduced	Reduced

*Morphology: . Gram negative to gram variable, motile or nonmotile rods. Diplococcus forms predominate in solid media. Bipolar staining common, may be encapsulated.

Colonies: White, glistening, smooth, moist; may have pink or yellowish tint.

male infant was admitted to the hospital with multiple sites of osteomyelitis in the distal metaphysis of the left radius, upper metaphysis of the right humerus, and upper metaphysis of the left femur (Figs. 1 and 2). Serologic tests for syphilis were negative. *B. anitratum* was isolated from the blood. Therapy with broad-spectrum antibiotics resulted in clinical and roentgenographic recovery. Table I summarizes some of the features of these cases.

DISCUSSION

General considerations and bacteriology. Bergey places the tribe Mimea in the following classification based on the work of De Bord:

Class	Schizomycetes
Order I	Eubacteriales
Suborder I	Eubacteriineae
Family XI	Parvobacteriaceae
Tribe IV	Hemophileae
Appendix	Tribe Mimeae (De Bord)
Genera	Mima
	Mima polymorpha species
	Mima polymorpha var. oxidans (variant)
	Herellea
	Herellea vaginicola (Bacillus anitratum is a member of this species)
	Colloides
	Colloides anoxydana species

These organisms are gram-negative, pleomorphic, motile or nonmotile rods, often with bipolar staining. Some of their morphologic and biochemical characteristics are tabulated in Table II.[3] Members of the genus Mima are fairly inactive metabolically and do not ferment carbohydrates. Further, some strains are oxidase positive, a feature which may add to their mistaken identification as *Neisseria meningitidis.*

Herellea includes *B. anitratum,* which appears to be the same organism referred to by Schwab[4] as Bacillus W_5. This organism is citrate positive and ferments dextrose. It also produces acid with 10 per cent lactose but does not metabolize 1 per cent lactose.

Classification of these organisms by the use of specific antisera has not been completed, but well-defined somatic and capsular antigens have been demonstrated.

If a laboratory utilizes only morphologic methods in infections with gram-negative pleomorphic organisms, then members of the tribe Mimeae may be mistaken for various species of Neisseria.[5] Biochemical differentiation is possible in the routine laboratory and should be employed with severe infections in which there is a possibility that one of these organisms is the etiological agent. For primary isolation most strains of gonococci and meningococci are more fastidious than members of the tribe Mimeae, requiring enriched media to which blood, serum, or other substances have been added. Mimeae will grow readily, though sometimes slowly, in media employed for the isolation of enteric bacilli, such as MacConkey agar. Morphologically, the combined presence of gram-negative bacilli with gram-negative diplococci should suggest the possibility of one of these unusual infecting agents.

Clinical considerations.

M. polymorpha is not highly invasive and may be isolated from the vagina and the conjunctiva in normal individuals. However, infections may be produced by these organisms; these include vaginitis, conjunctivitis, skin infections, urethritis, genitourinary tract infections, chronic synovitis, septicemia, meningitis, and subacute bacterial endocarditis.[6-10]

The incidence of these infections is not known. De Bord demonstrated a surprising number of infections in which members of the tribe Mimeae were isolated. For example, in vaginal and conjunctival specimens from

Table III. Meningitis due to *M. polymorpha*

Author			*Treatment*	*Outcome*
De Bord		1948	Sulfadiazine	Survived
Schuldberg		1953	Penicillin, sulfadiazine	Died
Townsend	A	1954	Penicillin	Died
	B	1954	Penicillin, sulfadiazine	Survived
Olafson		1958	Penicillin, sulfadiazine	Survived
Fred		1958	Penicillin	Survived
Waite		1959	Sulfadiazine chloramphenicol	Survived

147 patients which contained gram-negative diplococci on smear, only 15 cultures revealed gonococci, whereas in 45 instances, members of the tribe Mimeae were isolated. Our observation of 7 cases within a period of 4 years suggests that severe infections due to these agents may be relatively common, even though only 7 cases of meningitis due to *M. polymorpha* have been previously recorded (Table III).[7, 11-15] As De Bord demonstrated, so-called "penicillin-resistant gonorrhea" may in some instances represent infection with members of the tribe Mimeae.

B. anitratum has been responsible for chronic synovitis and bacterial endocarditis and may be responsible for other infections.[16, 17]

Of the 7 reported cases of meningitis due to *M. polymorpha,* 5 occurred in adults and 2 in children.[11] The ages of our patients varied from a few days to 2 years. One might expect that the frequency of these infections might be relatively high in infants, because of the opportunities for exposure to these organisms in the birth canal. However, in our 2 newborn infants (Patients 1 and 2) we were unable to isolate *M. polymorpha* from the vagina of the mother or to demonstrate antibody to it in her serum. The poor defense of young infants against gram-negative organisms of low virulence may also be a factor contributing to infections in this age group.

Clinically infections with Mimeae may simulate those due to meningococci. Petechiae, purpura, and adrenal hemorrhage can occur in each. In our patients these findings were not observed.

The prognosis appears to be related to the severity of the infection, to the rapidity with which the offending organism is isolated, and to the administration of an appropriate antibiotic early in the course of the disease process. Three of our 7 patients died; the 3 were in the early neonatal period.

Antibiotic sensitivity patterns. The pattern of sensitivity is variable and cannot be predicted with any degree of accuracy for an individual strain and thus in vitro susceptibility tests should be performed in each instance. Most of the strains isolated have been resistant to penicillin; since these bacteria are often confused with Neisseria, this fact assumes special significance. There is only one reported instance of penicillin susceptibility. Most strains have appeared to respond to broad-spectrum antibiotics, especially oxytetracycline.

SUMMARY

Seven cases of severe infections (septicemia and meningitis) caused by organisms belonging to the tribe Mimeae are described. The offending species were *M. polymorpha* and *B. anitratum*. The ages of the patients varied from 4 days to 2 years. Three of the patients died.

One patient with septicemia due to *B. anitratum* had multiple foci of osteomyelitis. The bacteriologic and clinical aspects of these infections are discussed. Emphasis is placed upon the possibility of confusing infections with members of the tribe Mimeae with those caused by the gonococcus or the meningococcus.

We wish to acknowledge the cooperation of the medical technicians of the San Juan City Hospital.

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Autohemolytic anemia in young infants

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IDIOPATHIC autoimmune hemolytic anemia until recently was thought to be due to nonspecific antibodies, because the antibodies present agglutinated red blood cells with which they were tested regardless of the cellular group. Thus transfusion therapy was often complicated by the difficulty of finding suitable blood when cross-matching was attempted. Dameshek and Schwartz[1] in 1940 postulated that an antibody in the serum was the cause of the acquired hemolytic anemia. In 1946, Boorman, Dodd, and Loutit[2] found the direct Coombs test positive in some of their patients and thus proved the presence of a globulin antibody coating on the red blood cells. Further investigation has shown that the serum contains antibodies as evidenced by a positive indirect Coombs test. Kidd[3] in 1949 was able to elute the antibodies from the red blood cells and to demonstrate their presence by means of the indirect antiglobulin test.

It was not until 1953 that a specific antibody was first identified in autoimmune hemolytic anemia. Weiner, Battey, Cleghorn, Marson, and Meynell[4] were able to demonstrate anti "e" in the serum of a 32-year-old male with hemolytic anemia. His genotype was CD homozygous; thus it was obvious that in some unknown way he had produced an antibody against his own cells. Subsequently other workers[5, 6] have demonstrated various specific antibodies in autoimmune hemolytic anemia. The majority of these have been in the Rh system, although anti-Kell and anti-Duffy antibodies have also been incriminated. The seriousness of this disease is evidenced by the experience of Dausset and Colombani[7] in a series of 83 cases of idiopathic hemolytic anemia with warm antibodies: 54 per cent of these individuals recovered. Only 18 of the patients were tested for specific antibodies; they were demonstrated in 7. Of the 4 infants in the series, 3 died. Antibodies were not demonstrated in any of the 4. O'Connor, Vakiener, and Watson[8] reviewed the pediatric literature in 1956 and reported 18 additional cases in children under 5 years of age. Four of these died. There is no mention of specific antibodies in their patients, and it is assumed that none was found.

Therapy, which has included transfusions, steroids, and splenectomy, has not been conclusive. It appears that such therapy at best

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may support the patient until there is spontaneous recovery in the nonlethal cases. There have been no reports of cases due to specific antibodies in the young age group similar to the 2 described here.

CASE HISTORIES

J. M., a white male, 5½ months of age, was admitted to The Hospital for Sick Children in 1956 with a history of pallor and slight jaundice for 3 days. There had been no previous illnesses. As far as could be ascertained, the child had not received any drugs. The stools were of normal color, and the urine was pale brown. The liver and spleen were both slightly enlarged.

On admission the hemoglobin was 4.2 Gm. per cent and smears from the peripheral blood showed severe anisocytosis, poikilocytosis, and polychromasia. There were 12 nucleated red blood cells per 100 white cells and 17.8 per cent reticulocytes. The osmotic fragility of the red blood cells was moderately increased, with hemolysis beginning at 0.60 per cent sodium chloride solution. Bone marrow aspiration revealed increased cellularity with erythroid hyperplasia.

The infant's blood was group O, Rh positive (probably genotype cDE/cde); the direct Coombs test was positive. The serum contained a nonspecific agglutinin when tested against enzyme-treated cells, and antibodies with Rh specificity (anti-E and anti-f) when tested by the indirect Coombs test. The separation and nature of these antibodies are shown in Table I. A diagnosis of acquired hemolytic anemia with autoagglutinins was made. The course of the child's illness is shown in Fig. 1.

Because of the presence of Rh antibodies, the only blood found to be compatible with the child's serum when the tests were made by the indirect Coombs method was that of Rh genotype cDE/cDE. The infant was given a replacement transfusion of 1,000 ml. of blood, resulting in considerable improvement in his condition. Prednisone, 30 mg. per day, was also administered. The hemolytic process, however, continued unabated, and the infant's hemoglobin fell approximately 2.0 Gm. per cent per day. Duracton, 10 mg. daily, was substituted for the prednisone after 3 days; the Duracton was replaced by intravenously administered ACTH (10 mg. per day) after 9 days. During this time he required transfusion of an additional 1,000 ml. of concentrated red blood cells. There was no febrile reaction to the transfusions.

After approximately 2 weeks the hemolytic process appeared to be less severe, and Duracton, 5 mg. per day, was prescribed. The hemoglobin remained steady between 10 and 11 Gm. per cent. At this point his general condition was good and he was dis-

Table I. Serum, Patient J. M.

Cell panel	*20° C. papain*	*37° C. Saline*	*37° C. Albumin*	*Indirect Coombs*
CDe/CDe	+++(1:32)	–	–	++(1: 4)
cDE/cDE	++(1:16)	–	–	–
cde/cde	+++(1:32)	–	+(1:1)	+++(1:16)
CDe/cde	+++	–	+(1:1)	+++(1: 8)
CDe/cDE	+++	–	+(1:1)	+(1: 1)
cDe/cde	+++	–	+	+++(1: 8)
Serum absorbed with CDe/CDE cells				
CDe/CDe		–	–	–
cDE/cDE		–	–	–
cde/cde		–	Weak	++(1: 4)
cDE/cde –(pt)		–	–	++
Eluate from absorbing CDe/CDe cell				
CDe/CDe		–		++
cDE/cDE		–		–
cde/cde		–		++
CDe/cDE		–		+

Anti-E and patient's serum absorbed with CDe/CDe cells both agglutinated 77 out of 100 random group O cells.

Table II. Serum, Patient M. C.

	Test cells						
	CDe	*C^w cDe*	*cDE*	*cde*	*Cde*	*cDe*	*cdE*
Saline	–	–	–	–			
Albumin	–		–	–			
Papain	+	+++	+++	–			
I.C.T. 4°	+		+	+			
20°	+++		+++	–			
37°	+++		+++	–	–	+++	–
Eluate				–	–	+++	–
D. neut'd.*	–	–	–	–		–	

*Neutralized.

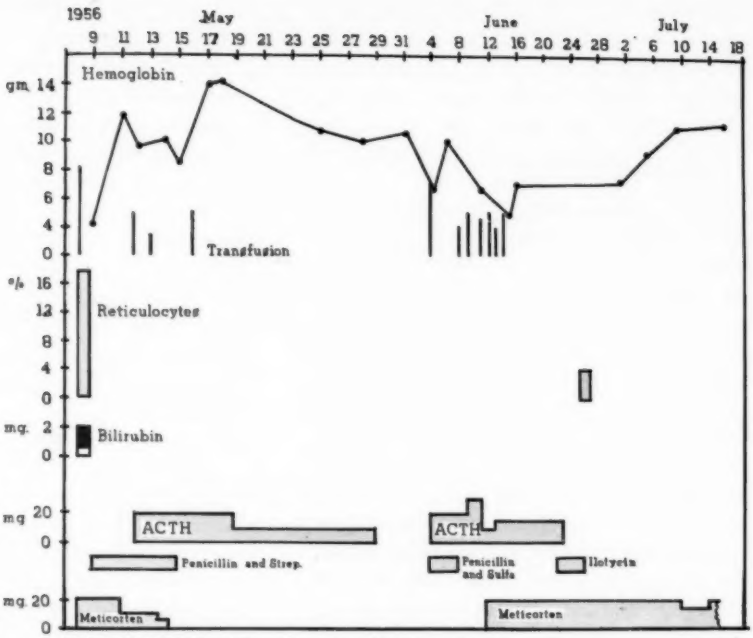

Fig. 1. Hospital course, J. M.

charged. Throughout the hospitalization the antibodies remained unchanged.

The patient returned 4 days later with an exacerbation of the hemolytic anemia. The responses to Duracton and to intravenous ACTH were again slow, and numerous blood transfusions were required. Eventually, after approximately 5 weeks, there was a remission of the hemolysis and the hemoglobin concentration rose spontaneously. Coincidentally, the antibodies disappeared from the serum. His illness had lasted about 10 weeks; since discharge he has been well.

M. C., a 2½-month-old white male infant, was admitted to The Hospital in February, 1959, with a history of dark urine, jaundice, and anorexia for 3 days. The stools were brown. He had had no medication and no previous illness. The liver and spleen were both moderately enlarged.

The hemoglobin level was 3 Gm. per cent; the reticulocytes, 2 per cent. There was a slight polymorphonuclear leukocytosis, and an occasional spherocyte was seen on smear. The osmotic fragility was slightly increased. The mother's blood group was O, Rh positive (CDE). The child was group O, Rh positive (CDe) probably heterozygous. The Coombs test was negative. The infant's blood was cross-matched without any difficulty with that of a CDe donor, and he was given 400 ml. of blood during the next 3 days. At the end of this time, the hemoglobin was still only 5.6 Gm. per cent; it was obvious that he was destroying the transfused cells rapidly. The serum was again tested, and he was found to have a weakly positive Coombs test and Rh antibodies with a specificity of "D" (Table II). He was then given Rh-negative blood which maintained the hemoglobin at a higher level. His hospital course is shown in Fig. 2.

Prednisone, 20 mg. daily, was begun on the second hospital day and was increased to 30 mg. after 2 weeks. The reticulocyte count remained low throughout this period, and the hemoglobin fell gradually. Bone marrow aspiration on two occasions showed increased cellularity with marked erythroid hyperplasia. Because of the possibility of a block in maturation, folic acid was begun about

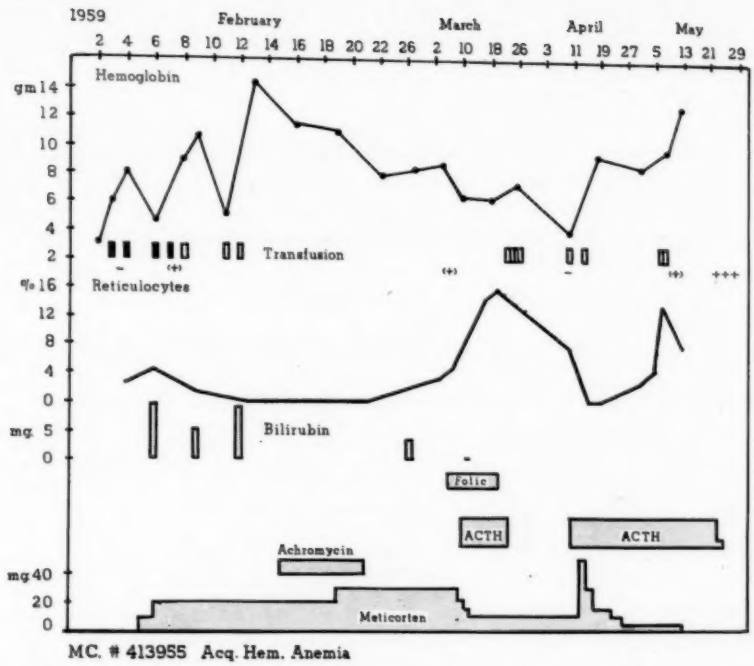

Fig. 2. Hospital course, M. C.

the sixth hospital week and also 4 days later Duracton, 20 mg. per day. There was an excellent reticulocyte response but even after 3 weeks the hemoglobin level continued to fall. When it reached a level of 4.0 Gm. per cent, further transfusions of Rh-negative blood were given. The patient was discharged on prednisone therapy with a hemoglobin of 9 Gm. per cent after 8 weeks of hospitalization.

He was readmitted 2 weeks later with a hemoglobin level of 4 Gm. per cent and a low reticulocyte count. The Coombs test was again negative but subsequently became positive again. The serum revealed the same "D" antibody. He was transfused with Rh-negative blood and Duracton was again administered. There was no reticulocytosis, and the hemoglobin level continued to fall during the following 3 weeks. It had been decided to perform a splenectomy, but the reticulocyte count was found to be increased on the morning of the scheduled operation and it was cancelled. Subsequently there was a rapid rise in both reticulocytes and hemoglobin, with the hemoglobin rising 7 Gm. per cent within 10 days. The Coombs test became negative and the antibody disappeared. The infant had been sick for approximately 3 months (Fig. 2).

DISCUSSION

These 2 cases are unusual. Each infant had specific autoantibodies against his own red blood cells; yet the clinical courses were much shorter than is customary in adults. In each instance the course of the disease was unaffected by therapy. Following the spontaneous remissions, the antibodies disappeared in the same mysterious fashion in which they had appeared. The second case presents even more unanswered problems. For example, why was the Coombs test negative on admission? Furthermore, it is doubtful that the anti "D" was present on admission, since, if it had been, it would not have been possible to cross-match the patient's blood with that of the CDe donor. The negative Coombs reaction on subsequent testing might be explained by the fact that the great majority of the cells at that time were Rh-negative ones.

The etiology of this condition is obscure. Chown and Lewis[9] have suggested two possible mechanisms: (1) An unknown viral antigen in the red blood cell might be able to produce an antibody so similar to the Rh antibody that the red cell antigen might react with it. They were able to demonstrate antibody of C^w specificity in the blood of one of 9 patients in the early stages of infectious hepatitis. (2) The virus might alter the antigen in the red blood cell or act similarly to a hapten and form a new complex antigenically foreign to the host. The antibody thus produced could then spread out slightly and affect the red cell.

Another possibility is that the individual suddenly loses a tolerance for his own red blood cells as a result of some change in the antibody-forming cells of the body. It has been suggested recently that endogenous proteins such as those of the lens, sperm, and thyroid can on occasion become antigenic to the individual's own tissues. It has also been suggested that the antibodies are a consequence of the hemolysis rather than its cause. Although this theory is not widely held, it is possible in the second case, where the Coombs test was negative on admission, and the antibodies were probably not yet present as they were not demonstrable when first tested. This might have been an intermediate stage. Then substances released by the hemolysis of the red blood cells might become slightly altered and become antigenic and produce an antibody against the patient's red blood cells. This antibody was then demonstrated by the usual methods.

SUMMARY

Two cases of autoimmune hemolytic anemia in very young infants have been presented, caused by autoantibodies of the Rh system. Each infant recovered spontaneously after several weeks' illness.

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The protein allowance in infancy and childhood

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THE problem of the "optimal" intake of protein in the growth period involves considerations difficult to assess in the human. In Slonaker's[1] study of the rat, the criteria of optimal growth, highest fertility, lowest mortality of offspring, and length of life were all best satisfied on an intake of 14.2 per cent of the calories as protein. Spontaneous activity was optimal on intakes a little higher, between 14.2 and 18.2 per cent. Objectives such as these are difficult to attain in cross-section human studies.

The interrelationship between nutrition and infection, however, has proved a fruitful source of information; it has been critically reviewed by Scrimshaw and associates.[2] Cannon's[3] studies relating the immune response to the diet, Dubos'[4] study on tuberculosis in the rat, Johnston's[5] study on tuberculosis in adolescents all correlated the course of the infection with the protein content of the diet.

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Adjustment to suboptimal levels of protein intake regularly occurs and involves, among other things, a fall in basal metabolic rate. This measurement is not feasible in infant studies. In a study of 27 children aged 4 to 14 years, we[6] were able to show that consistent positive balances of nitrogen were obtained when protein provided 15 per cent of an otherwise adequate caloric intake. At the 13 per cent level, the balance was usually, but not always, positive. At lower levels the nitrogen balance became negative and the basal metabolic rate fell, as Benedict had long before pointed out. Intakes of protein above 20 per cent of the calories were either refused or were noted to provoke nausea and vomiting. We had, we felt, described upper and lower limits to the intake of protein without establishing any figure as optimal.

In these long-term studies, the discordance between weight and nitrogen retention was evident. Long periods during which nitrogen was stored would be characterized by a flat weight curve, or even a loss in weight, and conversely weight might be gained during a period with a negative balance.

A sigmoid curve describes growth from conception to the end of the first year. The

Table I

	Protein (Gm.)	*Fat (Gm.)*	*Carbohydrate (Gm.)*	*Minerals (Gm.)*	*% calorie distribution*		
					Protein	*Fat*	*Carbohydrate*
Formula No. 1 (8% of calories from protein)							
45 Gm. Klim	12.02	12.60	17.10	2.610	8.0	18.9	73.1
95.5 Gm. Dextri-Maltose No. 2			92.53				
Water to equal 900 ml.							
Total N 1.92	12.02	12.60	109.63	2.610			
Formula No. 2 (13% of calories from protein)							
45 Gm. Klim	12.02	12.60	17.10	2.610	13	19	68
8.5 Gm. Casec	7.48	.17		0.380			
87.5 Gm. Dextri-Maltose No. 2			84.88				
Water to equal 900 ml.							
Total N 3.12	19.50	12.77	101.98	2.990			
Formula No. 3 (15% of calories from protein)							
45 Gm. Klim	12.02	12.60	17.10	2.610	15.0	19.2	65.8
12 Gm. Casec	10.56	.24		.540			
84 Gm. Dextri-Maltose No. 2			81.48				
Water to equal 900 ml.							
Total N 3.61	22.58	12.84	98.58	3.150			
Formula No. 4 (20% of calories from protein)							
45 Gm. Klim	12.02	12.60	17.10	2.610	20.0	19.5	60.5
20.5 Gm. Casec	18.04	.41		.920			
76 Gm. Dextri-Maltose No. 2			73.72				
Water to equal 900 ml.							
Total N 4.81	30.06	13.01	90.82	3.530			
Formula No. 5 (24.8% of calories from protein)							
45 Gm. Klim	12.02	12.60	17.10	2.610	24.8	19.7	55.5
28.5 Gm. Casec	25.08	.57		1.280			
68.5 Gm. Dextri-Maltose No. 2			66.44				
Water to equal 900 ml.							
Total N 5.95	37.10	13.17	83.54	3.890			
"Premature formula" (24% of calories from protein)							
Whole milk 500 ml.	17.0	19.0	23.0	3.500	24	26	50
Water 500 ml.							
Dextri-Maltose No. 2 60 Gm.			59.4				
Protolysate 30 Gm.	22.5			1.650			
Total N 6.31	39.5	19.0	82.4	5.150			

accelerative phase terminates at birth; from then on through the first year the rate of growth decelerates. The percentage of nitrogen retained from a given intake will follow this curve. Thus, amounts of protein giving rise to a positive balance at 1 month, when as much as 40 per cent of a given intake may be retained, may be inadequate at 6 months when the percentage of a given intake retained may be 15 per cent. In a premature infant, whose growth curve following birth will still be in the accelerative phase, Gordon and Levine[7] recorded retentions of nitrogen, expressed as percentage of intake, as high as 71 per cent with breast milk and 70 per cent with cow's milk feedings providing 2.8 Gm. of protein per kilogram. The percentage retention recorded by Stearns[8] for infants born at term on artificial feedings fell from 32 to 12 per cent throughout the first year.

We would agree with Wallace[9] that there are constant sources of error in the determination of the nitrogen balance and that these may be as much as 20 to 30 per cent

too high. Nevertheless, in the case of the long-continued balance studies that we have reported, the error can be presumed to be the same throughout an observation and a child may serve as his own control. In these studies these observations were made repeatedly: (1) Very high retentions of nitrogen might occur for periods of as long as 5 months with no gain in weight, followed by periods when the gain in weight followed an expected pattern with the retention of nitrogen proportionate to that associated with the formation of new tissue. (2) Conversely, gains in weight might be observed with steady losses of nitrogen over long periods of time. It is our concept that, within the limits of our ability to measure nitrogen retention, these large retentions noted in the beginning of the observations imply the replenishment of depleted "reserve" protein.

This brings up the question of "reserve" protein. "A reserve store of plasma protein building material is one subject for which the evidence is overwhelming and it may be accepted as a fact."[10] Madden and Whipple,[10] who make this statement, suggest that "reserve protein is that portion of the body protein that can be given up without interfering with body function." This is not conceived of as an isolated mass of nitrogenous tissue to be drawn on for emergency; rather, nitrogenous compounds appear to exist in a state of dynamic equilibrium reflected quantitatively to a degree in the serum protein levels. When a shift is made from an intake of protein on a low plane to a higher one, increased amounts of nitrogen will be retained up to a "physiologic ceiling" beyond which excretion will be increased and some of the intake will be represented by plasma nonprotein nitrogen. In the Minnesota study,[11] "active tissue" to the amount of 10 kilograms was regained in the recovery phase, although the percentage of protein in the body was practically unchanged. The largest shift percentagewise in the composition of the body was in water.

It is probably true in children as well as in the rat that no increase in the percentage of nitrogen in fat-free muscle can be effected by increasing the protein of the diet once maturation has occurred. But as one goes from a low plane to a full intake, there is a shift in the extracellular water content, as in the case of the Minnesota volunteers[11] from 33 to 24 per cent, a rise in fat from 5 to 15 per cent. In the beginning of the reconstitution of tissue, the weight curve might fall or remain level. In Bray's[12] study of 8 African children on marginal intakes the phenomenon of high retention of nitrogen with no gain in weight is noted when they received adequate protein.

The infant studies here reported had

Table II. Significance of balance data (formula No. 1 vs. Nos. 2 to 5 and "premature formula")

	Formula				
	2	*3*	*4*	*5*	*"premature"*
Caloric intake	$t = 0.37$ $p = > 0.70$ n.s.	$t = 5.63$ $p = 0.02$	$t = 5.63$ $p = < 0.01$	$t = 3.90$ $p = < 0.01$	$t = 3.96$ $p = < 0.01$
Weight gain (Gm./Kg./day)	$t = 1.88$ $p = 0.10$ n.s.	$t = 2.10$ $p = > .05$ n.s.	$t = 3.25$ $p = .02$	$t = 4.05$ $p = < .01$	$t = 0.65$ $p = > .50$ n.s.
Nitrogen intake (Gm./Kg./day)	$t = 12.18$ $p = < .001$	$t = 18.00$ $p = < .001$	$t = 28.12$ $p = < .001$	$t = 17.02$ $p = < .001$	$t = 29.23$ $p = < .001$
Nitrogen retention (Gm./Kg./day)	$t = 4.36$ $p = < .01$	$t = 3.82$ $p = < .01$	$t = 9.64$ $p = .001$	$t = 6.56$ $p = .001$	$t = 6.07$ $p = .001$
Weight gain Nitrogen retention (Gm./Kg./day)	$t = 5.16$ $p = < .01$	$t = 4.16$ $p = < .01$	$t = 6.82$ $p = .001$	$t = 7.84$ $p = .001$	$t = 6.28$ $p = .001$

n.s., not significant.

Table III. Infants under 60 days—45 three-day balances

Formula	*No. cases*	*Cal./Kg.*	*Weight gain (Gm./Kg. /day)*	*N intake (Gm./Kg. /day)*	*N retained (Gm./Kg. /day)*	*Weight gain N retained*
Formula No. 1 (8% of calories from protein)	7	135	11.2	0.430	0.251	45
Formula No. 2 (13% of calories from protein)	9	132	9.04	0.698	0.347	24
Formula No. 3 (15% of calories from protein)	14	121	8.12	0.736	0.335	24
Formula No. 4 (20% of calories from protein)	6	111	8.16	0.908	0.386	21
Formula No. 5 (24.8% of calories from protein)	9	114	6.18	1.128	0.520	12
"Premature" Formula (24% of calories from protein)	12	112	10.2	1.073	0.500	21

Means
0-20 days 21
21-40 days 19
41-60 days 18

rather simple objectives. We attempted to explore the level of retention of nitrogen at varying levels of intake, as we had in older children. We wondered whether satisfaction of appetite was a function of adequate calories or whether the composition of the food mixture influenced it. It is a clinical impression that infants on low-protein, high-carbohydrate mixtures are satisfied for shorter periods of time than those on higher-protein and lower-calorie mixtures. This may well be a consequence of the known tendency of high-protein diets to maintain blood sugar values at higher, more sustained levels than do relatively higher carbohydrate ones.

METHODS AND MATERIALS

Thirty-one normal male infants, all wards of a local social agency awaiting boarding home placement, were studied. The age range was 9 to 75 days. Each infant was fed a given formula for a 2 week period at the end of which time 3 day nitrogen balance studies were carried out. Collections were made on the usual type of metabolic frame. Glass adapters were fitted to the penis and urine was collected in a bottle containing xylol. Stools were collected in a container beneath a hole in the frame in which the buttocks rested. Stools were not marked but all stools passed during the 3 day period were considered an accurate 3 day collection. This assumes that the stool collected during the 72 hour period would contain the same amount of nitrogen as would that of a like period in which markers were used. Analytic methods have been previously reported.[13]

Infants were fed ad libitum one or more of six different isocaloric formulas in which the percentage of calories derived from protein varied from 8 to 25 per cent. Additional water was not offered. In order to keep the caloric content constant, increase in protein was accompanied by a decrease in the carbohydrate content of the formula, the percentage of fat being kept constant. Detailed composition of these formulas is given in Table I. The "premature formula" used for 12 infants was devised so that part of the nitrogen was derived from a protein hydrolysate. It will be noted that the "premature formula" contained 390 mg. per cent more mineral load than did formula No. 5.

Infants were placed on the different experimental formulas in a random fashion. The duration of most infants' hospital stay was such that each infant could be placed only on two or three of these formulas. Only 3 infants of less than 3,000 grams' weight were available for study.

RESULTS

The balance data are recorded for 67 observations to make them available for pooling with other material in the literature, but the number of variables is such, both in the composition of the feedings and in the growth potential at different ages, that statistical validity can be claimed only for the observations of infants under 60 days of age (Fig. 1).

The ad libitum caloric intake was significantly higher in infants fed formulas No. 1 and No. 2 than in those fed formulas Nos. 3 to 5, or the "premature formula." This suggests that satisfaction is achieved more readily on a higher than on a lower protein intake, and that larger volumes of the mixtures with a lower percentage content of protein are taken to compensate for this. Infants fed formulas Nos. 1 and 2 averaged 135 cal. per kilogram per day and 132 cal. per kilogram per day, respectively, whereas those fed the other formulas averaged 111 to 122 cal. per kilogram per day.

Significant differences in weight gain expressed in grams per kilogram per day were observed only between formula No. 1 and formulas Nos. 4 and 5. Those infants fed formula No. 1 gained 11.2 grams per kilogram per day, while those fed Nos. 4 and 5 showed average weight gains of 8.16 and 6.18 grams per kilogram per day, respectively.

Because of the higher protein content of formulas Nos. 2 to 5 and the "premature formula" the total nitrogen intake of infants fed these formulas was significantly greater than of infants fed formula No. 1. A concomitant increase in the amount of nitrogen retained, expressed in terms of grams per kilogram per day, was likewise found as the intake of protein increased from 8 per cent of the total calories to the next three levels. This increased nitrogen retention was significant, however, only when the 8 per cent protein formula was compared with those having 13, 15, and 20 per cent of calories deriving from protein. No significant difference in nitrogen retention was found when these latter three formulas were compared with one another (Table II). Of particular interest is the observation that, with the stepwise increase in the nitrogen content in formulas Nos. 2, 3, and 4 (deriving 13, 15 and 20 per cent, respectively, of calories from protein), there is a relatively constant relationship between weight gain and nitrogen retained, when each is expressed in grams per kilogram per day. This suggests the "physiological ceiling" noted in our study of the older children and also previously shown by Talbot and Gamble.[14] However, when 25 per cent of the calories are derived from protein (formula No. 5) an increase in nitrogen retention is observed, but this is accompanied by a decrease in weight gained per unit of nitrogen retained Tables III and IV.

These studies were carried out before the importance of the solute load presented to an infant's kidneys was appreciated, and measurements in this area were not made. In the light of these later developments, however, it is now felt that these infants when fed formula No. 5 probably developed

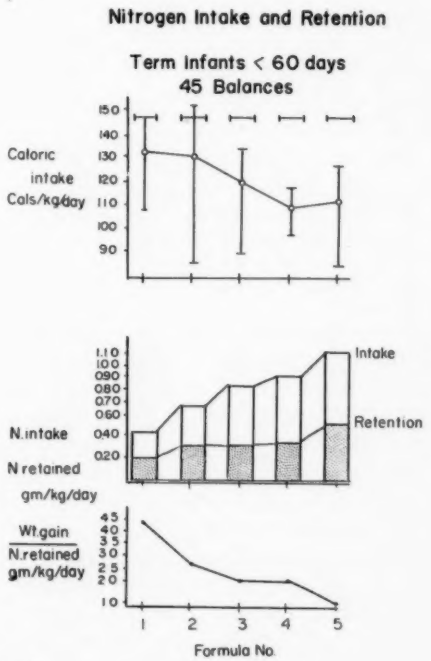

Fig. 1.

Table IV

Subject No.	*Age at start of diet*	*Weight at start of diet (Gm.)*	*Days on diet*	*Weight gain (Gm./Kg./day)*	*Intake (c.c./Kg./day)*	*Cal./Kg./day*	*N intake (Gm./Kg./day)*	*N retained (Gm./Kg./day)*	*Weight gained (Gm./Kg./day) / N retained (Gm./Kg./day)*
Formula No. 1									
1	19	4,083	12	12.4	197	130	0.415	0.288	43
2	25	3,177	19	10.7	192	127	0.405	0.227	47
3	11	3,084	18	11.9	215	142	0.452	0.279	43
4	29	3,658	12	9.15	228	151	0.480	0.258	36
5	9	3,092	27	10	197	130	0.414	0.227	44
6	13	3,714	19	11	199	131	0.419	0.254	43
9	52	3,319	18	14.1	202	133	0.425	0.226	62
7	75	5,644	12	5.6	168	111	0.220	0.120	46
8	66	5,445	3	5.1	180	120	0.382	0.208	25
Formula No. 2									
7	23	3,601	8	6.25	234	155	0.819	0.422	15
11	16	3,390	19	13.6	211	139	0.743	0.398	48
3	29	3,884	10	12.6	256	169	0.895	0.419	30
6	32	4,584	11	6.89	201	132	0.705	0.241	29
14	50	4,536	11	763	197	130	0.692	0.318	24
8	80	5,858	10	4.50	138	91	0.483	0.224	20
9	72	4,395	22	9.70	194	127	0.719	0.318	31
1	68	5,217	24	601	172	114	0.602	0.300	20
12	59	4,196	24	565	134	88.5	0.427	0.276	20
13	69	5,217	7	285	170	112	0.595	0.217	13
4	42	4,083	9	12.0	175	116	0.614	0.301	40
5	37	4,302	15	8.53	204	135	0.713	0.347	25
10	40	4,253	10	8.18	196	129	0.671	0.399	26
Formula No. 3									
17	1	3,714	22	16.9	200	133	0.804	0.350	48
11	5	4,508	17	9.2	174	115	0.700	0.330	28
3	38	4,579	12	4.25	194	128	0.779	0.292	15
13	35	3,999	24	8.75	205	137	0.830	0.434	20
16	43	4,013	6	2.88	172	113	0.690	0.289	10
18	23	3,629	9	12.6	201	133	0.807	0.416	30
19	31	3,454	10	4.17	198	131	0.792	0.331	13
20	26	3,913	6	11.6	177	117	0.709	0.297	40
25	16	4,545	11	10.3	140	93	0.564	0.290	36
15	31	3,799	13	14.5	201	133	0.809	0.348	41
12	53	4,714	16	2.27	162	107	0.646	0.339	7
4	51	4,607	6	−0.5	192	128	0.767	0.344	−1.45
5	54	4,834	9	9.10	171	113	0.681	0.226	40
6	50	5,188	11	7.59	180	120	0.719	0.410	19
Formula No. 4									
17	23	4,678	12	5.94	176	116	0.950	0.337	17
7	45	4,621	15	6.60	160	106	0.864	0.400	19
8	46	4,707	11	8.35	163	108	0.878	0.364	23
3	51	4,891	11	8.35	180	120	0.980	0.426	20
11	53	5,331	9	10.7	174	115	0.940	0.372	29

Table IV. Cont'd

Subject No.	*Age at start of diet*	*Weight at start of diet (Gm.)*	*Days on diet*	*Weight gain (Gm./Kg./day)*	*Intake (c.c./Kg./day)*	*Cal./Kg./day*	*N intake (Gm./Kg./day)*	*N retained (Gm./Kg./day)*	*Weight gained (Gm./Kg./day) / N retained (Gm./Kg./day)*
4	60	5,061	7	8.99	154	102	0.835	0.418	21
5	69	5,331	6	8.60	167	110	0.900	0.406	21
13	64	5,047	6	9.45	152	101	0.819	0.350	27
Formula No. 5									
21	17	4,451	8	8.90	170	113	1.090	0.556	16
22	19	3,233	7	9.89	164	110	1.065	0.559	18
23	24	4,877	7	3.65	196	130	1.280	0.601	6
16	33	3,489	10	11.1	185	122	1.200	0.661	17
24	37	3,941	8	9.05	175	117	1.155	0.371	24
4	56	4,799	6	5.93	193	127	1.260	0.653	9
13	58	5,018	5	-2.11	135	89	0.885	0.374	-6
8	59	5,117	9	5.15	173	114	1.120	0.380	14
7	60	5,245	17	4.07	169	111	1.098	0.521	8
5	63	5,245	6	0.44	188	124	1.224	0.704	0.62
13	83	5,673	11	3.14	167	110	1.110	0.542	5.8
"Premature formula"									
18	15	3,362	7.5	10.2	188	124	1.185	0.445	23
27	18	1,534	14	19	152	101	0.960	0.519	36
19	23	3,205	8	10.6	164	108	1.030	0.485	22
29	10	3,348	5.5	12.4	199	132	1.260	0.741	17
30	16	2,950	1.2	5.4	179	118	1.130	0.527	10
20	19	3,707	7	7.6	175	116	1.110	0.417	18
25	16	4,147	7	13.1	156	103	0.985	0.425	31
24	30	3,721	7	8.0	197	131	1.240	0.365	22
27	10	3,092	9	6.9	129	86	0.815	0.359	19
21	7	4,253	9	2.9	131	88	0.825	0.328	9
31	18	2,030	8	16.1	184	123	1.160	0.795	20
23	10	3,898	14	16.0	187	125	1.179	0.589	30

azotemia or hyperelectrolytemia and experienced secondary diminution of total body water. In retrospect, the clinical picture these infants presented was consistent with this conclusion. Apathy, increased regurgitation, and refusal were repeatedly observed by the nurse in charge of the study group. Clearly they did not tolerate the formula well, and this was in marked contrast to the other formulas studied. This idea is further supported by the fact that the "premature formula," which derived part of its nitrogen content from an amino acid hydrolysate with a lower ash content, was well tolerated by the infants. Moreover, nitrogen retention was approximately the same as that found on formula No. 5 but the ratio of weight gained per gram of nitrogen retained was comparable to that found with formulas Nos. 2 to 4. During these balance studies, the urine output of all infants exceeded 33 ml. per kilogram per day. Urinary nitrogen concentrations were less than 1,030 mg. per cent and calculated urea osmolar concentrations did not exceed 335 mOsm. per liter of urine. These figures are well within the limits of

safety for young infants as defined by Pratt and Snyderman[15] and Strauss.[16]

COMMENT

In the excellent review by Powers,[17] it is pointed out that the majority of successfully employed infant formulas contained protein to the extent of 10 to 20 per cent of the calories. In the system proposed by Von Pirquet, the commonly employed mixture with two-thirds of the calories derived from whole milk and one-third from added carbohydrate provided 15 per cent of its calories from protein. He felt that a mixture deriving only 10 per cent from protein was more suitable for the newborn but should not be employed beyond a month. In the light of studies of water and solute load in this age group this would be considered good practice today. With the passage of time and the deceleration of growth rate, however, 10 per cent becomes marginal in a few months. The percentage of protein is identical with that of sweetened condensed milk. With this milk Harrison[18] was able to demonstrate nitrogen retention, but his infants were also receiving cod-liver oil and orange juice. We have observed increased retentions of nitrogen following the introduction to the diet of both vitamins C and D as well as of the B complex. Accordingly it becomes impossible to make comparative studies of retention unless vitamin intake is also controlled. In our studies, no added vitamin supplement was used during collection periods.

CONCLUSIONS

1. Infants were fed isocaloric treated milk mixtures whose protein content provided 8, 13, 15, 20, and 25 per cent of the calories; the increase in calories from protein was compensated for by a comparable decrease in calories derived from carbohydrate. The increased intake of protein from 8 per cent to higher levels was accompanied by increased nitrogen retention; however, there were no statistically significant differences between the retentions on intakes of which the proportions of calories from protein were 13, 15, and 20 per cent, respectively. Higher retentions of nitrogen were noted with a diet containing 25 per cent of calories as protein, but in the absence of determinations of blood nitrogen the interpretation of the observation at this level is not possible.

2. Infants who received milk formulas containing a low percentage of calories from protein took significantly larger amounts of the formulas than did those who received mixtures with a higher percentage of protein.

3. The weight gained per unit of nitrogen retained is significantly higher on mixtures deriving 8 per cent of the calories from protein than on mixtures containing higher percentages of protein and lower percentages of carbohydrate. The differences are not significant when comparisons are made among mixtures deriving 13, 15, and 20 per cent of the calories from protein.

We are indebted to Mead Johnson & Company for preparing milk mixtures of varying composition. Dr. O. H. Gaebler supervised the balance determinations and Miss Rosemary Holland gave technical assistance. Dr. Annetta Kelly and Miss Ruth Sturrock did the statistical analysis. Mrs. Justine Viet was responsible for the collections of excreta in the nursery.

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Activity of acid phosphatase in the cerebrospinal fluid of children

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IN NORMAL infants and children the serum activity of acid phosphatase has been found to be greater than that of adults.[1] Furthermore, in certain pathologic conditions there are deviations from the normal range of serum acid phosphatase activity.[2]

In the present investigation total acid phosphatase activity was determined in the cerebrospinal fluid of children suffering from miscellaneous diseases.

SUBJECTS AND METHODS

The cerebrospinal fluid of 41 children admitted to the pediatric ward was studied on one or repeated occasions. The cerebrospinal fluid specimens were obtained by lumbar puncture, primarily for diagnostic purposes. Samples containing more than occasional red blood cells were discarded. If not examined within 2 to 4 hours after being drawn, the samples were stored under deep freeze conditions up to 3 days. According to our experience this does not affect the enzyme activity. Total acid phosphatase was estimated by the use of the method of King and Wooton[3] with the following modifications: The concentration of the substrate solution was M/50 instead of M/100. The reaction mixture consisted of: 0.5 ml. substrate solution; 1 ml. citrate buffer pH 4.9; 0.4 ml. cerebrospinal fluid, and 0.2 ml. distilled water. Acid phosphatase activity is expressed in King-Armstrong (K.A.) units. One King-Armstrong unit equals the amount of enzyme activity in 100 ml. serum which liberates 1 mg. phenol from disodium phenylphosphate after 1 hour's incubation at 37° C. at pH 4.9. If the cerebrospinal fluid contained many cells, the specimen was centrifuged and the estimation was performed on the supernatant. Cell counts were performed in a Fuchs-Rosenthal chamber, and protein was measured with sulfosalicylic acid according to Kingsbury and colleagues.[4]

RESULTS

The activity of total acid phosphatase in the cerebrospinal fluid of the children studied is recorded in Table I. It is evident from this table that, by the procedure used, acid phosphatase activity in children suffering from disorders, such as mongolism, mental retardation, congenital heart disease, gastro-

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enteritis, convulsions due to hypoparathyroidism or epilepsy was either nondetectable or only of low activity up to 0.3 K.A. unit. In infections of the respiratory system accompanied by fever it was found that the activity ranged between 0.07 to 0.98 K.A. units. In infective and/or space-occupying lesions involving the central nervous system, the activity ranged between 0.23 to 5.0 K.A. units. The enzyme activity was directly cor-

Table I. Activity of acid phosphatase in the cerebrospinal fluid in children suffering from miscellaneous diseases

Patient	*Age (years)*	*Sex*	*Diagnosis*	*Cerebrospinal fluid*		
				TAP (K.A. units)*	*Cells (No./cu. mm.)*	*Protein (mg./100 ml.)*
1	Newborn	M	Mongoloid	0	–	32
2	Newborn	M	Congenital heart disease	0	1	39
3	10/365	F	Pneumonia	0	0	–
4	3/12	F	Convulsions (hypoparathyroidism)	0	0	32
5	6/12	M	Gastroenteritis	0	2	23
6	8/12	M	Gastroenteritis	0	1	28
7	1 2/12	M	Edema of brain	0	2	66
8	1 9/12	F	Convulsions	0	1	22
9	2 3/12	M	Otitis	0	1	39
10	2 9/12	F	Mental retardation	0	–	12
11	2 8/12	M	Myelomeningocele	0	2	27
12	3	M	Headaches	0	3	28
13	8	F	Epilepsy	0	3	28
14	12	M	Epilepsy	0	6	22
15	7/12	F	Pneumonia	0.07	5	25
16	2	F	Brain abscess, recovering	0.2	4	89
17	2	F	Pharyngitis, otitis	0.2	1	20
18	9	M	Septicemia	0.2	2	17
19	4	M	Postmeningitis	0.23	2	15
20	8/12	M	Hydrocephalus	0.26	3	27
21	3/12	F	Convulsions (hypoparathyroidism)	0.3	1	29
22	6/12	F	Postmeningitis (E.K. II†)	0.3	39	33
23	9/12	M	Pyrexia of unknown origin	0.36	2	20
24	7	M	Encephalitis	0.4	1	17
25	1 3/12	M	Otitis	0.57	1	12
26	4/12	M	Cerebellar abscess (E.E. II)	0.6	650	100
27	8/12	F	Hydrocephalus	0.6	12	–
28	5/12	M	Pneumonia	0.67	2	25
29	4/12	M	Cerebellar abscess (E.E. I)	0.75	349	228
30	10	M	Septicemia	0.8	43	49
31	2/12	M	Septicemia	0.91	111	89
32	2/12	F	Paraplegia	0.96	1	41
33	9/12	M	Laryngitis	0.98	1	25
34	10	F	Tumor of third ventricle (L.S. I)	1.0	79	320
35	7/12	F	Meningitis (N.N. II)	1.09	–	–
36	7/12	F	Hydrocephalus, abscess suspected	1.2	95	58
37	8/12	F	Hydrocephalus	1.2	40	89
38	5/12	M	Cerebellar abscess	1.25	6	26
39	7	F	Cerebellar tumor	1.34	271	142
40	3	M	Meningitis	1.54	606	39
41	16	M	Cerebellar abscess	1.95	193	106
42	5/12	M	Subdural hematoma	2.0	160	388
43	10	F	Meningitis	2.6	17,000	625
44	7/12	F	Meningitis (N.N. I)	3.67	2	25
45	10	F	Tumor of third ventricle (L.S. II)	4.6	366	154
46	9/12	F	Meningitis (E.K. I)	4.9	–	122
47	11	M	Meningitis	5.0	2,547	68

*TAP indicates total acid phosphatase.

†Initials indicate patients in whom acid phosphatase has been repeatedly estimated. Roman numerals denote the order of determination.

Table II. Correlation between cerebrospinal acid phosphatase activity and white blood cell count

Cells (No./cu. mm.)	*Total acid phosphatase (K.A. units)*				*Specimens (No.)*
	0	*0 to 0.99*	*1 to 1.99*	*>2*	
0	2	0	0	0	2
0 to 5	9	13	0	1	23
6 to 50	1	3	2	0	6
51 to 100	0	0	2	0	2
101 to 300	0	1	2	1	4
>300	0	2	1	3	6
Total					43

Table III. Correlation between cerebrospinal acid phosphatase activity and protein concentration

Protein (mg./100 ml.)	*Total acid phosphatase (K.A. units)*				*Specimens (No.)*
	0	*0 to 0.99*	*1 to 1.99*	*>2*	
0 to 25	5	9	0	1	15
26 to 50	7	5	2	0	14
51 to 100	1	3	2	1	7
101 to 300	0	1	2	2	5
>300	0	0	1	2	3
Total					44

related with the activity of the disease process, decreasing upon recovery of the patient, as evidenced in 3 children in whom the cerebrospinal fluid has been tested repeatedly. (See Table I: Patient E. K., No. 46 and No. 22; Patient E. E., No. 29 and No. 26; Patient N. N., No. 44 and No. 35). This fact was further evidenced by the statistically significant correlation between total acid phosphatase activity and the white blood cell count or the protein concentration in the cerebrospinal fluid (Tables II and III). The correlation coefficient (r) between the number of cells per cubic millimeter and total acid phosphatase activity was: 0.455 ($p < 0.01$); and between protein concentration and the activity, 0.515 ($p < 0.01$). Exceptions to these correlations were Cases No. 33, No. 38, and No. 44, in which an increased total acid phosphatase activity in the cerebrospinal fluid was accompanied by a normal cell count and protein concentration.

COMMENTS

Although the mean serum total acid phosphatase activity in young infants is 6.24 ± 1.31 K.A. units,[1] no activity was detected by the method used in the cerebrospinal fluid of the newborn infants studied and in the infants without disease of the central nervous system. This finding may be due to the relative impermeability of the blood–cerebrospinal fluid barrier to protein under normal circumstances,[5] and may point to the fact that the nervous system is not a source of the increased serum total acid phosphatase activity in infancy and childhood. An increased activity was found in children with diseases of the central nervous system accompanied by an increased cell count and protein concentration. These findings are in accordance with those of Colling and Rossiter[6] who studied adults with meningitis, poliomyelitis, and syphilis. Unlike these authors, we found a direct relationship between total acid phosphatase activity and the number of cells and the protein concentration of the cerebrospinal fluid. The good correlation between the concentrations of protein and total acid phosphatase activity suggests that phosphatase may enter the spinal fluid in combination with a protein. As acid phosphatase has been demonstrated in the substance of the central nervous system,[7] it is impossible to assess the degree of contribution of brain tissue on one hand and of inflammatory cells on the other to the activity of total acid phosphatase in the cerebrospinal fluid. Since the preponderant type of cell encountered in the present study was the polymorphonuclear leukocyte, the assumption of Colling and Rossiter[6] that the lymphocytes are the main contributors to the increased acid phosphatase activity in cerebrospinal fluid cannot be readily accepted. Assuming that the polymorphonuclear leukocyte is a greater contributor of acid phosphatase than is the lymphocyte, it is easy to understand the good correlation between total acid phosphatase activity and the number of cells in the present study (predominantly polymorphonuclear leukocytes) and the lack of correlation between the activity

and the number of cells in the study of Colling and Rossiter[6] (predominantly lymphocytes). The low activity in children with disease accompanied by fever and of those who had no central nervous system involvement, as evidenced by physical findings and a normal cell count and protein concentration in the cerebrospinal fluid, may be due to a change in the permeability of the blood–cerebrospinal fluid barrier.[8] This mechanism could also explain the findings in Patients 33, 38, and 44 in whom increased total acid phosphatase activity was accompanied by a normal cell count and protein concentration.

Whether the measurement of total acid phosphatase activity in the cerebrospinal fluid would be of value as an aid to diagnosis in addition to the simpler measurements, such as cell count and protein concentration, cannot be concluded from this study.

SUMMARY

Total acid phosphatase activity has been estimated in the cerebrospinal fluid of 41 children.

Increased acid phosphatase activity was found in diseases of the central nervous system in which there was an increased cell count and protein concentration in the cerebrospinal fluid. The correlation between the total acid phosphatase activity and the number of cells and/or protein concentration was statistically significant. In some children with fever there was a slight elevation in the cerebrospinal fluid phosphatase activity.

The possible pathophysiologic mechanisms of the reported findings are discussed.

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Evaluation of transaminase activity in the cerebrospinal fluid in paralytic poliomyelitis

Preliminary report

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THE enzyme glutamic oxalacetic transaminase (GOT) is widely distributed in the tissues of the body; it is, however, highly concentrated in the myocardium, liver, brain, kidneys, and skeletal muscles.

In acute myocardial or hepatic lesions, the elevation of transaminase activity has been shown to correspond with the extent of the organic damage. By contrast, there is little information on serum transaminase levels in nervous disorders and particularly in poliomyelitis.

Production of experimental cerebral infarction in dogs, by injection of vinyl acetate into the internal carotid artery leads to marked increase in transaminase activity in the cerebrospinal fluid.[1, 2] This increase was found to be proportional to the severity and extent of cerebral infarction. Several workers have also found a significant increase in the transaminase of both cerebrospinal fluid and serum in patients with cerebrovascular disease, head injury, degenerative disease of the central nervous system, or convulsive disorders.[3, 4, 5] In most instances, no correlation was observed between the activity of transaminase and the concentrations of protein, sugar, glucose, and chloride in the cerebrospinal fluid[3, 6, 7]; nor has any been found between the serum transaminase activity and the enzyme activity of cerebrospinal fluid of the adults studied by Decker[6] and Green[7] and their associates.

Very little information is available as to transaminase activity in poliomyelitis; serum concentrations in 4 cases have been estimated by T. Paolo.[10]

The normal range of GOT activity of cerebrospinal fluid in adults who have no disease of the central nervous system has differed in various reports.[3, 4, 6-8] The values ranged from 0 to 12 units with a mean of

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Table I. Paralysis

Case No.	Age in months	Onset*	Duration (days before admission)	Type†			Site†								Degree
							Extremities								
							Upper		Lower						
				Meningeal	Encephalitic	Respiratory	Right	Left	Right	Left	Neck	Trunk	Abdomen	Bladder atony	
1	8	S	3	+	++	++			+	+	+	+			Extensive
2	12	S	3				±		++	+	+	+			Severe
3	6	S	4							±					Mild
4	24	G	8			++			±	+	+		±		Severe
5	8	S	4						++						Mild
6	18	S	7				±		++	+					Moderate
7	12	S	5					±	++	+					Moderate
8	14	S	5	+					±	+		±	±		Moderate
9	18	G	3				±		+	++				±	Moderate
10	6	S	5						+	+					Mild
11	36	S	3	+					+	+		+			Moderate
12	18	S	8						+	+		±	+		Moderate
13	18	G	12						++	++			+		Severe
14	7	S	16				±	±	+	+					Moderate
15	15	S	13						++	++		±	±		Severe
16	18	S	4							+					Mild
17	4	S	3					+	±	±					Mild
18	18	S	5				+		±	±					Mild
19	30	G	3	+	+			+		+	±	±			Moderate
20	12	S	3	+					+	++		±			Moderate
21	30	S	3	+	++		+		+						Moderate
22	24	S	1			+			++	++		±		+	Severe
23	20	S	2							±		±			Mild
24	20	S	10							+			±		Mild
25	10	G	7					+	+						Mild
26	12	S	15						+	++					Moderate
27	9	S	3						++	++					Moderate
28	3	S	2				+±			++				+	Moderate
29	12	S	3						+						Mild
30	9	S	2						±	++					Moderate
31	8	S	4						±	++		±			Moderate
32	12	S	2							++					Mild
33	11	S	3						+						Mild
34	6	S	3						+	++					Moderate
35	12	S	3	+	+				++	++					Severe
36	16	S	2						+	++					Moderate
37	12	S	2							+			+		Mild
38	14	S	2							+					Mild
39	12	S	2						+	++	+	+			Severe
40	9	S	3				+								Mild
41	9	S	3		+				++	++	+	+			Extensive
42	12	S	2						++			+			Moderate
43	12	S	1			±			±	++					Moderate
44	12	S	2				+								Mild
45	6	S	3							+					Mild
46	11	G	5				++		++	++	+				Extensive
47	18	S	2	+				++	++	++		+			Extensive
48	18	G	5					++	+	++	+	+			Extensive
49	18	S	4						+						Mild
50	9	S	1	+				±	±	+	+	±	±		Moderate
51	9	S	6							±			±		Miid
52	12	S	2						+	±			±		Mild
53	36	S	2						++	+					Moderate
54	11	G	4				+		++	++		+	+		Extensive
55	8	S	3					++	+						Moderate

*S, Sudden; G, Gradual. †±, Paralysis of only a few muscles of the part; +, Paralysis of about half of the muscles of the part; and ++, Paralysis of almost all muscles of the part.

Table II. GOT activity in cerebrospinal fluid in relation to duration of illness in mild cases of paralytic poliomyelitis

	GOT activity (units per milliliter) after onset of paralysis		
Case No.	*First week*	*Second week*	*Third week*
3		0	
5	0		
10		16	
16			0
17			0
18			0
23	56		36
24		0	
25		56	
29		24	
32		36	
33	36		
37	80		
38	80		
40		56	0
44	36		16
45		0	
49	16		
51		0	
52		0	0
Mean	43.4	18.8	7.43

6.8 units per milliliter in one report, from 4 to 40 units with a mean of 17 in another, and from 2 to 7 units with a mean of 5 units in a third report. The normal range for infants and children was not given.

In Egypt, U.A.R., poliomyelitis is becoming a problem. During the last few years, a large number of cases was reported; these included severe types and children of the upper age group.

In the present investigation GOT activity has been estimated in the cerebrospinal fluid of patients with acute poliomyelitis to determine: (1) whether there is an increase in transaminase activity, and (2) whether the degree of increased activity—if present—corresponds to the stage and/or severity of the disease.

ANALYSIS OF MATERIAL

For this purpose 55 children with clinically diagnosed acute paralytic poliomyelitis in Alexandria University Children's Hospital and 19 healthy children of the same age group were studied.

Analysis of cases.

Age. Four were between 3 and 6 months; 28 were between 6 and 12 months; 17 were between 1 and 2 years; 6 were between 2 and 3 years.

Sex. Thirty were males and 25 were females.

Season. These cases occurred from mid-November, 1959, to mid-February, 1960.

Feeding. A few infants were entirely breast-fed; the others received both breast and artificial feedings.

Nutrition. With the exception of 5 malnourished infants, all were moderately nourished.

Associated illness. In addition to paralytic poliomyelitis, 2 children (Cases 21, 47) had measles; 2 (Cases 8, 22) had pneumonia; 5 (Cases 10, 17, 30, 35, 51) had pharyngitis; 6 (Cases 5, 14, 23, 32, 40, 50) had gastrointestinal disturbances; and 1 (Case 21) had cardiac failure and measles. The last patient and one with respiratory paralysis (Case 1) died.

Table III. GOT activity in cerebrospinal fluid in relation to duration of illness in moderate cases of paralytic poliomyelitis

	GOT activity (units per milliliter) after onset of paralysis			
Case No.	*First week*	*Second week*	*Third week*	*Fourth week*
6	16.8			
7			0	
8			16	
9			16	
11		36		0
12			0	0
14	16			
19	16			
20		36		
21		36		
26	16			
27		36		0
28		2		
30	36			
31	36		0	
34			0	0
36		0		0
42		0		
43	80		16	
50		0	0	
53		16		16
55			16	
Mean	30.97	18	7.1	2.66

Initial febrile stage. In 16 of the cases (29.1 per cent), paralysis was the first noted manifestation with no fever preceding its onset; in 3 of these (Cases 5, 25, 34), however, fever appeared with the onset of paralysis. In 39 patients (70.9 per cent), paralysis was preceded by a febrile stage which varied in duration from 1 to 15 days with an average duration of 3.7 days. The fever subsided shortly before or at the time of appearance of paralysis in all but 10 patients, in whom it continued for some days, mostly as a result of associated illness.

Meningitic signs. Ten patients had mild or moderate rigidity of the neck (Table I); of these, 3 (Cases 1, 19, 21) also had encephalitic features.

The paralytic stage (Table I).

Onset of paralysis. In 8 patients the paralysis appeared gradually, whereas in 47 its onset was sudden.

Duration of paralysis before admission. This varied from 1 to 16 days, with an average of 4.3 days.

Extent and severity of paralysis. To facilitate evaluation of the results, the case material was divided into four groups, characterized as mild, moderate, severe, and extensive. In Table I the extent of the paralysis in the individual cases is indicated.

The degree and extent of paralysis were estimated after the acute phase, including muscle tenderness, had abated. Each of the four groups formed a fairly homogeneous clinical unit.

In the group with *mild* paralytic poliomyelitis, there were 20 patients whose paralysis was estimated to be ½ to 2 plus. From the 20 patients, 24 specimens of cerebrospinal fluid were obtained.

In the group with *moderate* paralysis, there were 22 children. The extent of their paralysis was estimated to be more than 2 and up to 4 plus; 31 specimens of cerebrospinal fluid were obtained.

The group with *severe* paralysis included 7 patients from whom 8 specimens of cerebrospinal fluid were obtained. The extent of their paralysis was graded as 4 to 6 plus.

In 6 patients the paralysis was considered to be *extensive,* or more than 6 plus. One specimen from each was examined.

A total of 69 specimens of cerebrospinal fluid were obtained from the 55 patients. When more than one specimen was taken from a given patient, at least one week separated the two withdrawals.

Table IV. GOT activity in cerebrospinal fluid in relation to duration of illness in severe cases of paralytic poliomyelitis

	GOT activity (units per milliliter) after onset of paralysis		
Case No.	*First week*	*Second week*	*Third week*
2	42		
4	36		
13			0
15			36
22	32		
35			16
39	56	80	
Mean	42	—	17.3

Table V. GOT activity in cerebrospinal fluid in relation to duration of illness in extensive cases of paralytic poliomyelitis

	GOT activity (units per milliliter) after onset of paralysis	
Case No.	*First week*	*Second week*
1	0	
41		80
46	36	
47	56	
48	36	
54	36	
Mean	32.8	—

METHOD OF TRANSAMINASE DETERMINATION

The method used was a modification of Dubach's[11] which is a modification of that of Karmen and La Due.[12] Initially, 0.5 ml. of serum or cerebrospinal fluid is pipetted into a test tube, mixed with 0.5 ml. of transaminase substrate, and the tube is left for half an hour at 20° C. Then one drop of 100 per cent trichloroacetic acid and 2 drops of aniline citrate reagent are added and the tube left for another 20 minutes at the same temperature. Then 0.5 ml. of 2:4

Table VI. The mean values of GOT activity of the four groups with varying degrees of paralysis during the first few weeks after the onset of paralysis

Grouping of cases on basis of severity of paralysis	*First week*		*Second week*		*Third week*		*Fourth week*	
	No. of samples	*GOT units/ml.*	*No. of samples*	*GOT units/ml.*	*No. of samples*	*GOT units/ml.*	*No. of samples*	*GOT units/ml.*
Mild	7	43.40	10	18.80	7	7.43	–	–
Moderate	7	30.97	9	18.00	9	7.10	6	2.67
Severe	4	42.00	1	80.00*	3	17.30	–	–
Extensive	5	32.80	1	80.00*	–	–	–	–
Mean GOT		37.00		24.29		8.84		2.67

*Single determination.

dinitrophenyl hydrazine reagent is added, the contents of the tube are well mixed, allowed to stand for 15 minutes, and then extracted with 2 ml. of toluene. The toluene extract is separated by means of a microseparating funnel, and 1 ml. of this extract is taken in a clean test tube and mixed with 3 ml. of 2.5 per cent alcoholic potash. The reddish-violet color produced is matched against a control made by the same amounts of reagents and using the same amount of serum or cerebrospinal fluid mixed with a drop of trichloroacetic acid, which depresses any enzyme activity present; the tube with the test material is treated similarly. The matching is carried out with a Unicum electric colorimeter with a filter at a wave length of 550 m.u. The colorimeter is first adjusted by setting the galvanometer at 100 with the control; the reading is then taken of the "sample" tube. The concentration is calculated by referring to a standard curve made by using a very pure sample of sodium pyruvate. Series of different concentrations were made, ranging from 12 to 70 gamma per milliliter (using the stoichometric equivalent amount of sodium salt, 1 Gm. = 1.25 Gm. of sodium salt; pure pyruvic acid is unsuitable because of its instability). The readings are plotted against concentrations which yielded a straight line.

One SGOT unit is defined as the activity of 1 ml. of serum which will form the same color complex in 20 minutes at 25° C. as 1 μg per milliliter of pyruvic acid.

Transaminase activity in the cerebrospinal fluid was determined on admission of the child to the hospital and wherever possible about a week after that. Its activity in the serum was also estimated at the same time in some cases. The time of taking the samples differed from 1 to 25 days from the onset of paralysis and so the figures are classified under the corresponding week subsequent to such onset.

The cerebrospinal fluid of 19 normal healthy infants and children of the same age group (4 to 36 months) was also examined for transaminase activity to serve as controls. All of them were foundlings attending the child welfare center of the hospital.

Table VII. GOT activity in cerebrospinal fluid and serum from 12 cases of paralytic poliomyelitis. Samples taken within first week following paralysis

Case No.	*GOT activity (units per milliliter)*	
	CSF	*Serum*
43	80	16
44	36	0
45	0	36
46	36	0
47	56	0
48	36	0
49	16	0
27	36	0
50	0	80
55	16	0
54	36	80
53	16	0

DISCUSSION OF RESULTS

Controls. No transaminase activity was detected in the cerebrospinal fluid of any of the 19 healthy infants and children used

as controls.* These results do not agree with those obtained from healthy adults, in whom values from 0 to 40 units per milliliter had been reported.[3, 4, 6-8] It was shown by Decker[6] and Green[7] and co-workers and is confirmed by our data (Table VII) that there is no relation between serum transaminase values and those of cerebrospinal fluid. This is presumably due to the blood-brain barrier.

Patients with mild degrees of paralysis. Of the 24 specimens examined from 20 patients, 7 were taken during the first week following paralysis, 10 during the second, and 7 during the third week. The mean values for GOT activity were 43.40, 18.80, and 7.43 units per milliliter, respectively. It is evident that the enzyme activity is highest in the days immediately following the onset of paralysis (Table II).

Patients with moderate degrees of paralysis. The 31 specimens obtained from the 22 patients were distributed over the first 4 weeks of the disease as follows: 7, 9, 9, and 6 specimens for the first, second, third, and fourth weeks, respectively (Table III). The corresponding mean values were 30.97, 18.00, 7.10, and 2.67 units per milliliter. These results confirm the greater activity of GOT during the acute phase of the illness. Compared with those obtained from the mild cases, they show no correlation with the severity of paralysis in the first few weeks of the disease.

Patients with severe degrees of paralysis. Only 8 specimens from the 7 patients were examined. Four samples were examined during the first week of illness, the mean of which was 42.00 units per milliliter; one sample during the second week had a value of 80 units per milliliter; and 3 samples during the third week had a mean value of 17.30 units per milliliter (Table IV). Though the number of specimens is small, the results in general conform with those of the two previous groups.

Patients with extensive paralysis. From the 6 patients, five specimens were obtained during the first week following paralysis (mean 32.80 units per milliliter); one, during the second week (80 units), and none during the third and fourth weeks (Table V). Although the data are insufficient for analysis, they do support the lack of correlation between the height of GOT activity and the severity of paralysis (Table VI).

Variations of GOT activity in relation to duration of paralysis. It will be noted in Table VI that, with the exception of the two values for the second week in the severe and extensive groups, the values are highest during the first week, and diminish progressively in the subsequent weeks. The mean values for the 4 weeks were 37.00, 24.29, 8.84, and 2.67 units per milliliter, respectively. If the two figures for the second week in the severe and extensive groups are excluded because each of them represents a single determination (Tables IV and V), then the corrected mean values will be 37.00, 19.37, 8.84, and 2.67 units per milliliter for the first 4 weeks, respectively.

The increased transaminase activity in the cerebrospinal fluid is presumably due to damage of the nervous tissue. It is known that the virus of poliomyelitis may produce myocarditis during the stage of viremia.[11, 12, 13] It is also the impression of some workers[14, 15] that subclinical liver damage is an essential part of this disease, although others[16, 17] have not confirmed this observation. Such involvement could explain the increased activity of GOT in the serum but not in the cerebrospinal fluid. In Table VII it will be noted that there was an increase in enzyme activity in the cerebrospinal fluid in all but 2 patients, whereas there was measurable GOT activity in only 4 of the same 12 patients when serum and cerebrospinal fluid specimens were examined simultaneously. These data suggest the possibility of a blood-brain barrier, and also suggest that the increased GOT activity in the cerebrospinal fluid is the result of destruction of nervous tissue by the virus.

It is well known that the extent and severity of paralysis in the first few weeks of the disease do not always correspond with

*Nine additional children were investigated later; none of them had evidence of transaminase activity in the cerebrospinal fluid.

the extent of nervous tissue damage or with the extent of residual paralysis. Similarly, we observed no correlation between the severity of paralysis in the first few weeks of the disease and the height of activity of GOT (Table VI).

It may be that the height of activity of GOT has a relation to the amount of destroyed nervous tissue. If so, it may provide an estimate of the expected residual paralysis and thus be of prognostic value. This hypothesis will be the subject of a subsequent publication.

SUMMARY

The cerebrospinal fluid of 55 patients with acute paralytic poliomyelitis and of 19 healthy children (9 additional ones at a later date) as controls was examined for glutamic oxalacetic transaminase (GOT) activity.

On the basis of severity of paralysis, the cases were clinically classified as mild, moderate, severe, and extensive. The data suggest that:

1. The cerebrospinal fluid of healthy infants and young children has no measurable GOT activity.

2. In most cases of acute paralytic poliomyelitis there is a rise in transaminase activity in the cerebrospinal fluids, especially during the first one or two weeks following the onset of paralysis, suggesting the possibility of injury to the nervous tissue.

3. The increased transaminase activity of the early phase of the disease gradually declines to normal.

4. The height of transaminase activity showed no correlation with the severity of the disease.

5. No correlation has been found between the serum transaminase and that of the cerebrospinal fluid in cases of paralytic poliomyelitis.

We are greatly indebted to Dr. Fardous Labib of the Department of Hygiene and Preventive Medicine for the statistical analyses quoted in the paper, and we are grateful to Dr. Salah Hammad and Mr. M. Maher for their valuable help.

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Pulmonary resection for tuberculosis in children

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WITH the advent of effective antibacterial drugs the over-all prognosis for tuberculosis in children has improved; there is a far better outlook in regard to complications and mortality. In the majority of instances pulmonary lesions in children have a benign evolution when diagnosed early and adequately treated; the pulmonary and lymph node foci usually heal without sequelae. Nevertheless, there remain cases in which the antibacterial treatment must be complemented by surgical procedures. In some circumstances such as delayed diagnosis, adverse social conditions, reinfections due to massive and repeated contagion, and/or inadequate or incomplete treatment, the disease follows a progressive course with the production of vast destructive lesions. In some instances the parenchymatous and lymphatic foci enlarge, become caseous and necrotic and cavities may ensue, whereas in others the lesion becomes encapsulated and surrounded by fibrous tissue with calcified deposits. There are occasions when the caseous material ruptures into a bronchus, resulting in bronchogenic dissemination. In other instances an enlarged lymphatic node compresses a bronchus and produces atelectasis.

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Many of the lesions mentioned do not respond to the usual antituberculosis therapy, or, if they do, there are caseous, fibrotic, or bronchiectatic changes, or cavitation.

The final outcome of these severe processes in which extensive pulmonary destruction has occurred is unfavorable.[1-6] Even when fibrocaseous foci have been sufficiently encapsulated they remain as reservoirs of bacilli that may sooner or later become active again and grow progressively less responsive to drug therapy. In some instances in which medical treatment has been successful in overcoming the tuberculous infection, the sequelae are so vast and disabling that the child cannot lead a normal life. It is in these instances that pulmonary resections are indicated to eliminate the destroyed pulmonary tissue which constitutes the main source of tuberculosis in the adult.

We recognize that surgical treatment of pulmonary tuberculosis in children is justified in only a minority of instances and that with improvement of preventive and curative measures the need for surgical treatment will decrease progressively.

The first major lung operations for pulmonary tuberculosis in children in Chile were performed at the L. Calvo Mackenna Hospital in 1949.[17] Here we submit a report of our experience in 106 pulmonary resections performed on 105 children from March, 1950, to December, 1958. Almost all of the resections were done by one of us (H. W. J.).

MATERIAL

Frequency. During the period from 1950 to 1958 covered in this report, 1,261 tuberculous patients were admitted to the wards of the Calvo Mackenna Hospital; in 105 of these a pulmonary resection was deemed necessary.

Age. Table I shows the age distribution of the children who were operated upon. Most of them were 6 to 14 years of age, with an average age of 10.3 years.

Sex. Table I also shows the distribution by sex; 46 were male and 59 were female.

Preoperative diagnosis. As noted in Table II the indications for operation were principally fibrocaseous processes, with or without cavities, and bronchiectasis. Resections were also performed for chronic cavities, caseous pneumonia, large tuberculomas and/or indurated areas, epithelized cavities, and in one instance extensive persistent atelectasis.

In 77 cases the lesions were considered to be active, and in 28 inactive, but with sequelae that hindered a normal life.

Previous therapy. Of the 77 children with active tuberculosis all had been treated intensively with the drugs currently available for a period of at least 6 months and in some instances as long as 3 years. Some had also had collapse therapy, but without success. Thus these children were referred to our hospital with vast and destructive lesions that had not responded to treatment.

Among the 28 children with inactive tuberculosis, 11 had had thorough treatment, which had been unsatisfactory in 5 cases; 12 had not had antimicrobial therapy prior to operation.

Known time of evolution of the tuberculous pulmonary lesion before operation. As can be seen in Table III, the known time of evolution of the tuberculous process before pulmonary resection in the 77 children with active lesions was in the majority of instances more than 6 months and as much as 10 years. The 3 patients with lesions of less than 6 months' duration were operated upon on an emergency basis, 2 because of massive hemoptysis and 1 because of a cavity which had ruptured into the pleura.

In all the 28 inactive cases the preoperative period of observation was more than 3 years.

Surgical procedures. The types of operative procedures are shown in Table IV; left pneumonectomies were performed three times as frequently as right ones, whereas right lobectomies were twice as frequent as left. In only one patient was a bilateral resection performed; the right and left lower lobes were resected in a two-stage operation.

The high proportion of pneumonectomies in comparison to segmentary resections is striking, but it is explained by the frequency with which extensive lesions were encountered in our patients.

Anesthesia was administered in all instances by endotracheal intubation with ether and d-tubocurarine. The operations were performed with the child in the prone

Table I. Age and sex distribution

Age	*Sex*		*Status of tuberculous lesion*	
	Male	*Female*	*Active*	*Inactive*
Up to 2 years	1	2	2	1
2 to 6 years	6	7	7	6
6 to 14 years	39	50	68	21
Total	46	59	77	28

Table II. Types of tuberculous lesions*

Active tuberculosis (77 cases)		
Fibrocaseous processes		27
Fibrocaseous processes with cavities		25
Chronic cavities		12
Caseous pneumonia		7
Tuberculoma and/or indurated areas		6
Secondary lesions:		
Bronchiectasis	22	
Fibrothorax	16	
Atelectasis	2	
Inactive tuberculosis (28 cases)		
Bronchiectasis		25
Epithelized cavities		2
Atelectasis		1
Secondary lesions:		
Fibrothorax	6	
Extensive fibrosis	5	
Atelectasis	3	

*Several patients had more than one type of lesion.

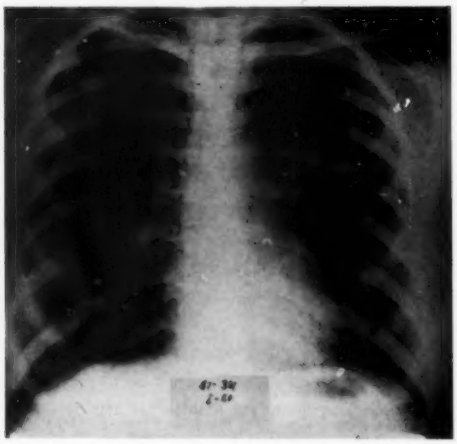

Fig. 1. Tuberculous cavity of the upper left lobe.

position, until it was found that the lateral position was more convenient.

In all cases the approach was through a posterolateral incision; initially this was followed by a costal resection and subsequently by a simple intercostal thoracotomy through the fourth, fifth, or sixth intercostal space according to the location of the lesion.

In the majority of instances pleural adhesions were found, especially in the area of the upper lobe. Following complete liberation of the lung, the site and extent of the lesion were determined by careful palpation and checked with the clinical and radiologic data in order to determine the magnitude of the resection.

When the pulmonary hilum was dissected, the arteries were ligated first if possible, then the veins, and finally the bronchus, leaving the stump uncovered by the pleura. On only 2 occasions because of firm hilar adhesions was it necessary to ligate the pulmonary vessels in the pericardial sac.

In the lobectomies it was the policy to leave two Malecot tubes, each communicating with a flask with sealed underwater drainage, but without aspiration. In the pneumonectomies a Malecot tube was also inserted, but left closed, only to be opened if a displacement of the mediastinum occurred. These tubes were kept in place for 24 to 48 hours, and antibiotics were injected intrapleurally through them.

In 21 of the 28 pneumonectomies, intrapleural Lucite ball plombages were performed 15 to 20 days after the operation through a small incision under local anesthesia in the fourth or fifth intercostal space at the level of the anterior axillary line. Only completely sealed capsules were used.

The routine postoperative medication consisted in maintaining the antituberculosis drugs, other antibiotics, nasal oxygen, and blood or electrolyte solutions according to the clinical condition of the patient and to laboratory tests.

Complications. Of the 105 children operated upon, 17 developed complications,

Table III. Duration of active lesions prior to operation

Duration	*No. of cases*
<6 months	3
6 months to 1 year	19
1 to 2 years	20
2 to 3 years	13
3 to 4 years	9
4 to 5 years	4
5 to 6 years	3
6 to 7 years	4
7 to 8 years	1
8 to 9 years	0
9 to 10 years	1
Total	77

Table IV. Resections performed

	Right	*Left*	*Total*
Pneumonectomies	7	21	28
Lobectomies	48	23	71
Superior	17	13	
Superior and median	5		
Superior and inferior	2		
Superior and upper segment of inferior lobe	3		
Superior, and segments of median and inferior lobes	1		
Median	9		
Median and inferior	8		
Lingula and inferior		3	
Inferior	2	6	
Bilateral (inferior lobes)	1	1	
Segmental resections	5	2	7
Total			106

Table V. Mortality

Years	No. of cases	Deaths			
		Immediate	Delayed	Total	%
1951-1952	26	4	1	5	19.2
1953-1954	17	0	1	1	5.9
1955-1956	15	0	2	2	13.3
1957-1958	47	0	0	0	0
Total	105	4	4	8	7.6

10 of which occurred in the 2 weeks following operation (immediate complications) and 7 at a later date (delayed complications).

Among the 10 immediate complications, there were 3 bronchopleural fistulas with bronchogenic dissemination; one of these children died.

These children were among the early ones and had extensive lesions with bronchial involvement; now such lesions would be regarded as contraindications to surgery. Two children developed contralateral reactivation, and one of them died. They had advanced bilateral tuberculosis that had partially improved under medical treatment and thus were considered for surgical treatment.

Two children developed bronchogenic dissemination as a result of the intervention but recovered. One child died during the operation from an anesthetic accident, one died following staphylococcus pneumonia, and another developed pyogenic empyema from which he recovered promptly.

Of the 7 delayed complications, in 4 there was reactivation of remaining lesions. Two of these children died, one as the result of a bronchial fistula; 2 who had hemoptysis recovered.

Mortality. Of the 105 children, 8 have died (7.6 per cent). During the years 1951-1952, when the indications for surgery were not as well established and isoniazid was not available, there were 5 deaths in 26 operations (19.2 per cent). The other 3 deaths occurred prior to 1957 (Table V). One was due to an anesthetic accident and the other 2 to a reactivation of the tuberculous process that did not respond to therapy. During the last 2 years there have been no deaths in 47 operative cases.

Follow-up. Figs. 1 to 8 show examples of pulmonary lesions operated on successfully. Following the operation each child was treated with antituberculosis drugs for a minimum period of 6 months. For the first 2 or 3 weeks the child remained in the hospital from which he was transferred to

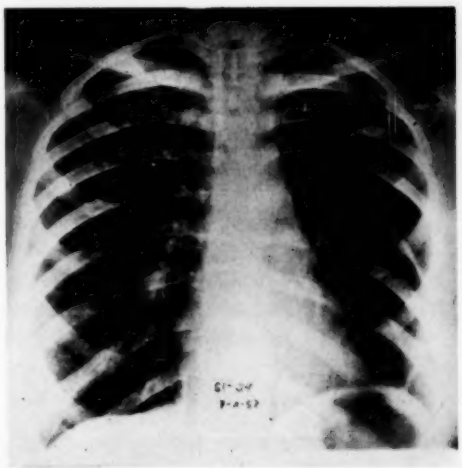

Fig. 2. The same case as shown in Fig. 1, 20 months after resection of the left superior lobe.

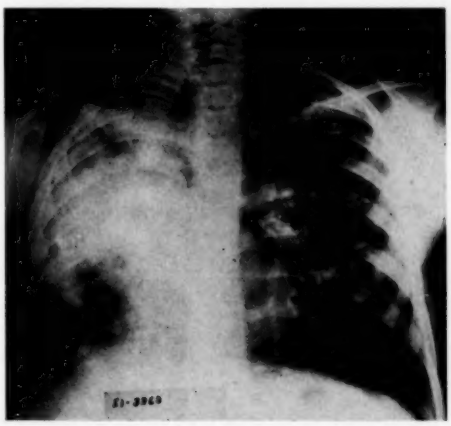

Fig. 3. Fibrocaseous tuberculosis with cavity on the right side. Nodular dissemination on the left side.

a sanatorium for 6 to 12 months. Subsequently all have attended our outpatient department, so that their records extend over a period of 3 to 8 years postoperatively. As stated above, only 7 children developed delayed complications that made rehospitalization necessary.

There were no chest deformities or changes in pulmonary capacity in the children who had lobectomies or segmentary resections. Of those subjected to pneumonectomy, 7 had no Lucite ball plombage and in 3 cases, because of delay in performing this procedure, only a few spheres (5 to 7) could be left in place. In these children there were major displacements of the heart and mediastinum, pulmonary hernias, and/or costal and skeletal retractions that could not be corrected by physiotherapy.

These 10 children were the first ones operated upon (1951-1952). In the following 18 pneumonectomies, Lucite ball plombage was performed at an earlier date, 15 to 20 days postoperatively; in these cases the outcome was satisfactory, and there have been no permanent deformities.

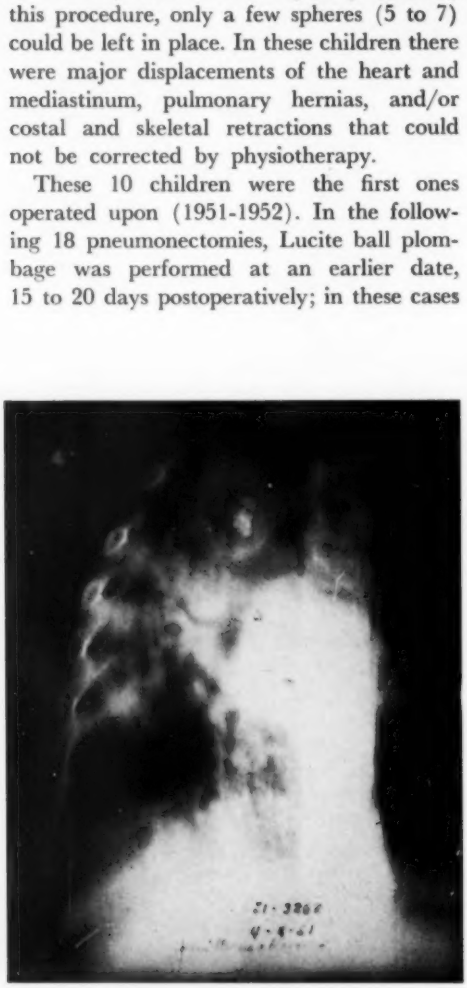

Fig. 4. Same case as shown in Fig. 3. Planigraphy of the right side showing a destructive process with calcifications and bronchiectasis.

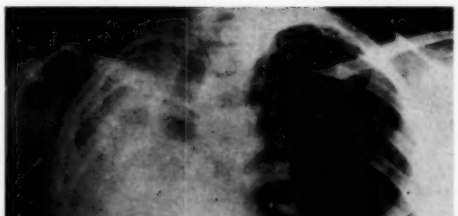

Fig. 5. Same case as shown in Figs. 3 and 4, seven months after right pneumonectomy. Left side normal. Deviation of mediastinum.

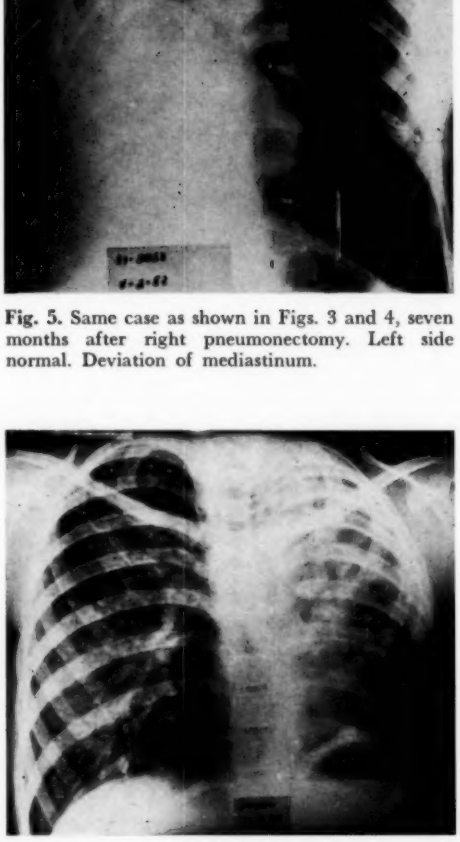

Fig. 6. Fibrocaseous tuberculosis with cavities of the left lung.

DISCUSSION

Most often pulmonary tuberculosis in children responds satisfactorily to standard treatment with the antimicrobial drugs available. The consensus is that when after prolonged treatment there remain active tubercle bacilli in the lungs there is the possibility of a relapse. In such a situation surgical treatment, when feasible, is the

only means of eliminating the necrotic or infective tissues.[7-16] Unfortunately, not all cases are amenable to surgery. After several mishaps in our earlier experience, we now have greater confidence in defining the indications for operation: (a) advanced fibrocaseous lesions, with or without cavities, which after intensive medical treatment do not improve and in which activity persists; (b) single cavities, which persist in spite of drug therapy, pneumothorax, bronchial aspiration, and nebulization therapy (in our experience these cavities have had fibrotic walls innerlined with epithelium and were situated near the hilum or in a position in which drainage was difficult); (c) caseous pneumonia which involves at least one segment or lobe and has not responded to prolonged treatment; (d) tuberculomas, which we consider as primary caseous lesions, surrounded by fibrotic tissue; when multiple these lesions are also called "areas of induration" and are usually resistant to drug therapy; (e) extensive atelectasis which has not improved after intensive treatment consisting of antituberculosis drugs, corticosteroids, bronchial aspirations, postural drainage, and nebulization therapy; (f) bronchiectasis complicating active or inactive tuberculosis, if the lesions are extensive or localized in lobes where drainage is poor and may result in reactivation of the tuberculosis or in invalidism; (g) fibrothorax, a chronic pleuropulmonary lesion, also an indication for surgery since it may lead to bronchiectasis, destruction of lung tissue, extensive fibrosis, changes in the topography of intrathoracic organs, and skeletal deformities. In most of our cases of fibrothorax we have found active tuberculous nodes which were resistant to drug therapy.

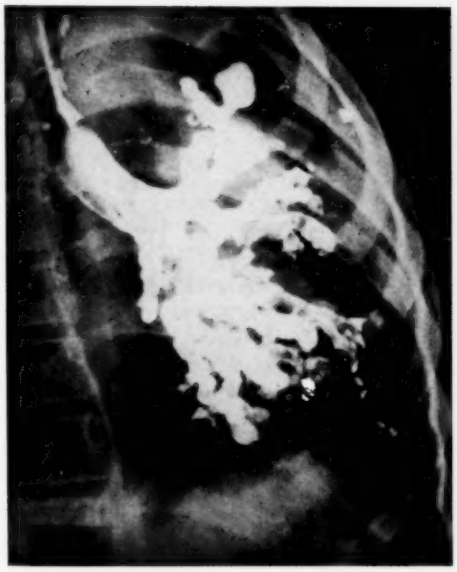

Fig. 7. Same case as shown in Fig. 6. Bronchography reveals bronchiectasis.

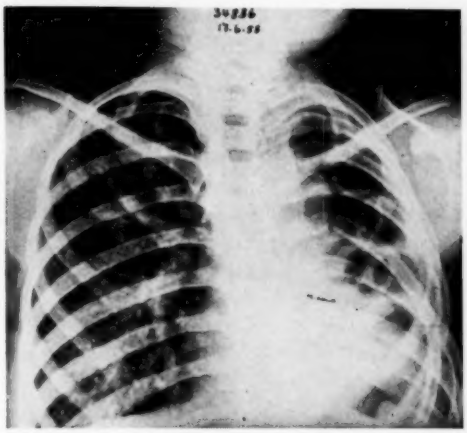

Fig. 8. Same case as shown in Figs. 6 and 7, thirty-five days after left pneumonectomy and Lucite ball plombage.

There are two definite contraindications to pulmonary resection in pulmonary tuberculosis in children: (a) active lesions in the other lung, and (b) bronchial tuberculosis in the lung in which the operation is considered.

In nearly all instances in which surgery is contemplated we observe the child for at least 6 months under full antituberculosis therapy, in order to ascertain whether the lesion is irreversible and also to enable all exudative processes to subside, become more circumscribed and less active. There are two situations which are considered as emergencies: (a) superficial cavities that per-

forate into the pleura, producing empyema and hemothorax, and (b) repeated hemoptysis that cannot be stopped with medical treatment.

Bearing in mind the two contraindications mentioned above, we have no hesitation in advising surgical removal of diseased tissue not amenable to thorough medical treatment. These lesions are a constant menace; at best they are a source of ill health resulting in prolonged hospitalization and in death within two or three years. More commonly a more rapid deterioration from spread of the disease or from intercurrent infection materially shortens the survival period.

SUMMARY

Most cases of pulmonary tuberculosis in children respond to the available antituberculosis drugs; nevertheless, there are some in which this treatment fails, and there are important residuals. Pulmonary resection is indicated in some of these cases; the present report deals with the experience in 106 resections performed at the Calvo Mackenna Hospital. On the basis of this experience, indications and limitations for this type of surgery are suggested.

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"Diaper rash," a diagnostic anachronism

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THE term "diaper rash" is used all too frequently in a diagnostic sense, as though the diverse dermatoses that may affect the young child constituted a single, specific clinical entity. Treatment based on this meaningless, purely topographic diagnosis tends to defeat its purpose. A skin condition, no matter what its location, requires a specific differential diagnosis, so that optimal treatment may be given. The present study proposes to illustrate this point on the basis of the response of 256 young children with candidal and noncandidal diaper dermatoses to medications containing specific anticandidal agents and to nonspecific medications. Four of the remedies used were evaluated by means of a double-blind study involving 98 patients.

As a result of constant irritation and slight maceration engendered by wet diapers, the skin in that area becomes a fertile soil for a variety of dermatoses.[1] Many of these are clinically characteristic. Ammoniacal dermatitis and candidiasis are seen with great frequency, and each requires a differential diagnosis.

Ammoniacal dermatitis combines an unmistakable smell with skin eruptions on the convex surfaces of the areas in contact with wet diapers. The eruptions may be erythematous or become lichenified, or they may consist of reddish-purple, occasionally eroded vesicopapules.[2] This condition is easily differentiated from pyoderma, allergic reactions, or miliaria rubra, and from less specific conditions, such as seborrheic or atopic dermatitis, that are not limited to the diaper area.

Candidiasis of the diaper area occurs far more frequently than has long been assumed.[3] It is now known that conditions previously diagnosed and depicted in many textbooks, as "intertrigo" (another topographic term) are frequently candidal in origin. This predilection for the intertriginous areas of the body serves to distinguish a candidal from an ammoniacal dermatitis.

In many infants cutaneous candidiasis is a concomitant or a sequela of oral thrush. The stools, invariably infected with *Candida albicans* in these cases, are considered the focus of cutaneous infection in the diaper area.[4-6]

The typical candidal "diaper rash" presents more or less widespread erythema on the buttocks, lower abdomen, and inner aspects of the thighs, often with fissuring in

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Table I

		Patients (No.)
Cream A	0.1% triamcinolone acetonide in cream base containing 5% propylene glycol	26
Cream B	0.1% triamcinolone acetonide, plus, per gram, 2.5 mg. neomycin 0.25 mg. gramicidin 100,000 units nystatin in cream base containing 5% propylene glycol	29
Cream C	Lanolin and silicone in aqueous vanishing cream	20
Cream D	Nystatin, 100,000 units per gram, in cream base containing 5% propylene glycol	23

the intertriginous areas. A border of characteristic "white-collared" satellite lesions and vesicopapules marks the region of active spread of the infection. More rarely, the condition may be generalized and involve other areas of the body as well, including the scalp. In severe cases erythema and exfoliation may be so pronounced as to simulate Leiner's disease.[7]

Demonstration of *Candida albicans* in direct examination and in cultures from the lesions is pathognomonic for cutaneous candidiasis, since the organism rarely, if ever, occurs on the skin as a saprophyte (Fig. 1).[6, 8] Laboratory diagnosis should, therefore, be resorted to wherever possible and, especially, in cases where differentiation of cutaneous candidiasis from such conditions as seborrheic dermatitis or infantile (atopic) eczema may present difficulties.[3] The candidal "diaper rash" is thus a common, specific dermatitis with usually clear-cut clinical features substantiated by valid laboratory evidence, both of which facilitate the differential diagnosis.

Therapy of all types of diaper dermatoses should obviously include elimination of extraneous factors that favor eruption, such as infrequent change of diapers; infrequent exposure to air; harsh, irritating detergents, alkalies or bleaches in home laundering; and the prolonged wearing of rubber or plastic panties. Diarrhea and frequent loose stools, a common cause of skin irritation, should be treated. Here, also, candidal etiology should be ruled out.[9] Topical medication should counteract inflammatory reactions and protect the skin from excess moisture. Over and above these nonspecific measures

Table II. Response of candidal and noncandidal diaper dermatoses to medications containing specific anticandidal agents

Vehicle	*Anticandidal agent (per gram of vehicle)*	*Other ingredients (per gram of vehicle)*	*Candidal dermatoses*			*Noncandidal dermatoses*		
			Total No. of cases	*Improved*		*Total No. of cases*	*Improved*	
				No.	*%*		*No.*	*%*
Ointment I plasticized liquid petrolatum base	Nystatin, 10^5 units	None	27	23	85	—	—	—
Cream D*	Nystatin, 10^5 units	None	14	10	71.4	9	4	44.4
Cream B*	Nystatin, 10^5 units	Triamcinolone acetonide 0.1% Neomycin 2.5 mg. Gramicidin 0.25 mg.	16	14	87.5	13	12	92.3
Ointment II plasticized liquid petrolatum base	Nystatin, 10^5 units	Fludrocortisone, 0.1% Neomycin 2.5 mg. Gramicidin 0.25 mg.	30	27	90.0	14	12	85.7
Dusting powder S	Nystatin, 10^5 units	Neomycin 2.5 mg. Gramicidin 0.25 mg.	18	18	100.0	24	21	87.5
Dusting powder N	Nystatin, 10^5 units	None	6	6	100.0	6	5	83.5
Ointment III plasticized liquid petrolatum base	Amphotericin B, 2%	None	15	12	75.0	—	—	—

*Tested in double-blind study.

Table III. Response of candidal and noncandidal diaper dermatoses to nonspecific medications

Vehicle	Other ingredients (per gram of vehicle)	Candidal dermatoses			Noncandidal dermatoses		
		Total No. of cases	Improved		Total No. of cases	Improved	
			No.	%		No.	%
Cream A*	0.1% Triamcinolone acetonide	13	2	15.4	13	5	38.5
Cream C*	Lanolin Silicone	13	4	30.8	7	4	57.1
Dusting power T	None	6	1	16.7	12	8	66.6

*Tested in double-blind study.

and remedies, to which many textbooks limit their recommendations, the candidal infection requires specific antimycotic medication.

The present study is based upon a double-blind evaluation of four creams. Two of these contained nystatin and may be considered specifically anticandidal; 2 were nonspecific in that they lacked antimycotic ingredients.

The results obtained in this blind study were then compared with those obtained with other, known, ointments and dusting powders.[10, 11]

METHOD

The test preparations were arbitrarily designated A, B, C, and D, respectively, by a person not connected with the study, who sealed one tube each into paper bags numbered 1 to 100. The investigator prescribed each preparation by number, the code letter and nature of the medication remaining unknown to him until completion of the study. Bias in the choice of any one of the medications was thus prevented.

After completion of the study the medications were identified and found to have been distributed as shown in Table I.

MATERIAL

Ninety-eight patients were treated with the test medications. None of the patients was toilet trained. In all of them the dermatosis had been present for at least one week and had failed to respond to various home remedies. At the beginning of the test period the mothers were instructed concerning proper diaper management, restriction of the use of rubber or plastic panties, and frequent exposure of the child's buttocks to the air. Uniform conditions of treatment and elimination of extraneous sources of irritation were thus achieved as far as practically feasible.

The period of treatment was set arbitrarily at 7 days. This time was deemed sufficient, in the light of previous observations, to judge whether or not the medication was clinically effective.[10]

Cultures for *Candida albicans* were taken from the affected areas before and after therapy in all cases. Only patients with posi-

Table IV

Medication	Contents	Patients (No.)
Ointment I	100,000 units nystatin per gram of ointment base consisting of 95% liquid petrolatum plasticized with 5% polyethylene	27
Ointment II	0.1% fludrocortisone, plus 2.5 mg. neomycin sulfate, 0.25 mg. gramicidin, 100,000 units nystatin, per gram of same base as above	44
Ointment III	2% amphotericin B per gram of same base as above	15
Dusting powder S	100,000 units nystatin, 2.5 mg. neomycin, 0.25 mg. gramicidin per gram of talcum powder	42
Dusting powder N	100,000 units nystatin per gram of talcum powder	12
Dusting powder T	Unmedicated talcum powder	18
Total		158

Table V

	Candidal	*Non-candidal*	*Total*
Treated in course of blind study	56	42	98
Treated with known medications	102	56	158
Total	158	98	256

Table VI. Comparative response of noncandidal diaper dermatoses to medications with and without antibacterial antibiotics (neomycin, gramicidin)

Medication	*Total No. of cases*	*Improved*	
		No.	*%*
*Antibiotics present**			
Cream B	13	12	92.3
Ointment II	14	12	85.7
Powder S	24	21	87.5
Total	51	45	88.2†
*Antibiotics Absent**			
Cream A	13	5	38.5
Cream C	7	4	57.1
Cream D	9	4	44.4
Powder N	6	5	83.5
Powder T	12	8	66.6
Total	47	26	55.3†

*See Tables II and III for ingredients

†The difference between these 2 percentages, 32.9 per cent ± 8.5† per cent, is statiscally significant, being more than 3 times larger than its error.

tive cultures were considered "candidal." Since the study was concerned principally with the problem of treatment of cutaneous candidiasis, diaper dermatoses of other etiology were collectively classified as "noncandidal."

The number of candidal and noncandidal dermatoses treated with each of the four test preparations is shown in Tables II and III.

EVALUATION OF RESULTS

Only two categories for evaluation were recognized. "Improved" denotes considerable to complete regression of the lesions in the course of one week. "Failure" denotes slight to no regression or aggravation of the condition. The term "cure" was avoided deliberately, since in general no diaper dermatosis can be regarded as completely and permanently cured until toilet training has been well established and the underlying conditions favoring these skin eruptions have been removed.

The results obtained in the blind study were then evaluated and compared with those obtained with the medications as listed in Table IV.

In all, 256 patients were studied. Candidal and noncandidal dermatoses were distributed as illustrated in Table V.

RESULTS AND DISCUSSION

It should be noted that the 98 patients treated in the course of the blind study were unselected in regard to the etiology of their skin condition and represent a random sample of the diaper dermatoses seen by one physician in the course of one year. The fact that more than 50 per cent of the diaper dermatoses seen during that time were of candidal etiology agrees with Robinson's[3] observations and attests to the frequency of this condition.

The therapeutic results of the present study are summarized in Tables II, III, and VI, and in Fig. 2. They indicate very clearly that candidiasis of the diaper area requires specific anticandidal therapy. This fact is illustrated in Fig. 2 which charts the comparative over-all rates of improvement of

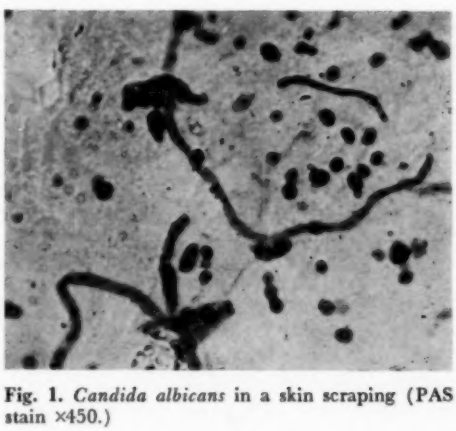

Fig. 1. *Candida albicans* in a skin scraping (PAS stain ×450.)

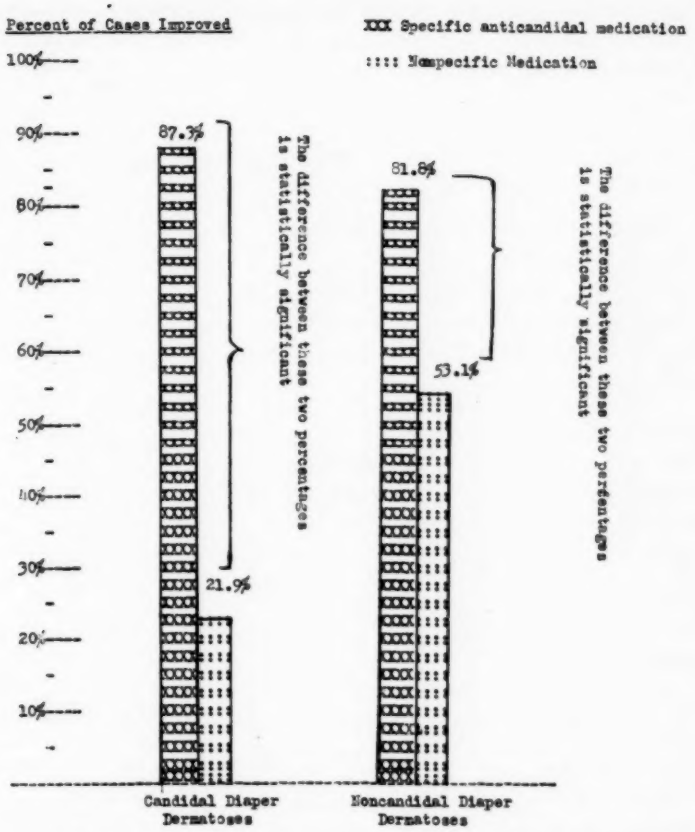

Fig. 2. Over-all rate of improvement of 256 candidal and noncandidal diaper dermatoses with specific anticandidal and with nonspecific medications.

candidal cases treated with anticandidal agents (87.3 per cent) and similar cases treated with nonspecific remedies (22 per cent). This poor rate of improvement indicates that soothing medications, designed merely to counteract inflammation, are of little use in a candidal infection, and are only moderately effective in noncandidal dermatoses (53 per cent).

The therapeutic effect of anticandidal agents appears to be somewhat enhanced by the presence of antibacterial antibiotics.

Marked clinical improvement was noted in all candidal and in most noncandidal dermatoses with medicated dusting powders (Table II). Unmedicated talcum powder gave fair results in noncandidal eruptions and poor results in candidal ones (Table III). These results indicate that the protective mechanical action of talcum powder alone has little effect in candidiasis, unless a specific antimycotic agent is incorporated into this vehicle. This necessity is further illustrated by the poor results obtained with the two nonspecific creams in candidal infections (Table III).

The response of noncandidal dermatoses to the two preparations containing a steroid, nystatin, and antibacterial antibiotics (Table II) was excellent. Analysis of these results indicates that this response was due neither to nystatin nor to the steroid, since preparations containing each of these substances alone were not markedly successful (Table II, Table III). Table VI summarizes this reaction of the noncandidal diaper der-

matoses to medications with and without antibacterial antibiotics. The over-all improvement rates with these two types of medication are 87.7 per cent and 45 per cent, respectively, and the difference between the two percentages is statistically significant.

SUMMARY AND CONCLUSIONS

Candidiasis of the diaper area is a common dermatitis with characteristic clinical manifestations and pathognomonic laboratory findings which permit differential diagnosis.

The condition requires specific antimycotic therapy. This is shown by a blind evaluation of two anticandidal and two nonspecific medications in 56 cases of candidal and 42 cases of noncandidal diaper dermatoses, and comparison of the results with the therapeutic effects of known anticandidal and nonspecific remedies in an additional 158 cases of candidal and noncandidal eruptions.

The over-all improvement rate of candidal dermatoses with specific remedies was 87.3 per cent, as against 22 per cent with nonspecific remedies.

In the noncandidal conditions, medicated dusting powders, ointments, and creams containing antibiotics were superior to nonmedicated powder and to vanishing creams with or without steroids.

The concept of "diaper rash" as a distinct clinical entity should be abandoned, since it may lead to faulty diagnosis and inadequate therapy of skin eruptions in young children. Each diaper dermatosis requires specific diagnosis and appropriate therapy, as illustrated by the experience described here with candidiasis of the diaper area.

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Thyroid enlargement probably induced by cobalt

A report of 3 cases

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THE effectiveness of cobaltous chloride in the correction of such anemias as those of chronic infection,[1, 2] chronic renal disease,[3] prematurity,[4] sickle cell disease,[5] and pregnancy[6] has been documented. However, attention has been repeatedly called to the potential dangers of cobalt therapy. The most frequent untoward effects have included nausea, vomiting, and anorexia; less frequent have been skin eruptions, tinnitus, nerve deafness, substernal pain, flushing of the face and extremities, and thrombocytosis.

Reports of the goitrogenic action of cobalt began appearing in 1955 following the relatively frequent use of an iron-cobalt preparation.† Although the goiter disappears and thyroid function returns to normal when administration of cobalt is discontinued, it is apparent that the use of cobalt preparations presents definite limitations.

Three instances of goiter apparently induced by cobalt have been recognized on the Pediatric Service of Vanderbilt University Hospital during the past 5 years, the most recent one being in July, 1960.

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CASE REPORTS

Case 1. T. B., born March 2, 1955, weighed 2 pounds, 7 ounces and was cyanotic at birth. At 2 days of life he was started on 13 mg. of cobaltous chloride daily for 3 days and then 24 mg. daily thereafter because of a hemoglobin value of 9.5 Gm. per 100 ml. Because of labored respirations and marked intercostal retractions, the infant was placed in an incubator and given oxygen and high humidity until the fifth day when oxygen was discontinued. Thereafter, until the sixty-third hospital day, his course was unremarkable except for one episode of cyanosis which was felt to be the result of aspirating formula. About 30 minutes before he died, the patient had been offered a feeding which in part was refused. He became cyanotic and respirations ceased. Despite oxygen, caffeine sodium benzoate, and intracardiac adrenalin, the infant died.

Autopsy performed at Vanderbilt Hospital* showed that both lungs were firm. The

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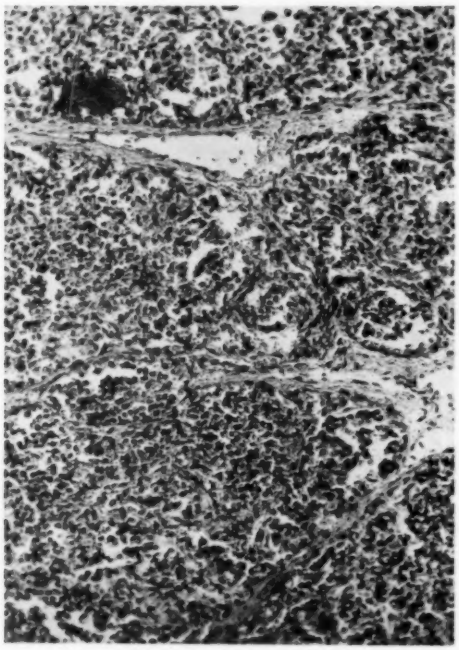

Fig. 1. Case 1. Photomicrograph showing thyroid hyperplasia with abnormal acinar formation. (Original magnification ×100.)

thyroid was large and weighed 8.5 grams. The gland felt soft and somewhat edematous. No nodules were seen or palpated. There was no mention of tracheal compression. Microscopically, the sections of pulmonary tissue showed early diffuse interstitial pneumonitis. There was hyperplasia of the thyroid (Fig. 1) with little apparent attempt at acinar formation. The gland appeared to be separated into large lobules by fibrous tissue septa. Within these lobules there were numerous cells with a small amount of eosinophilic cytoplasm and large basophilic nuclei. Because of the long duration of treatment with cobalt-iron preparation and the known properties of the medication to produce thyroid hyperplasia, it was felt that the coexistence of these two findings in the case was more than mere coincidence. No other cause for the enlargement could be found, although congenital goitrous cretinism could not be excluded as a possibility.

Case 2. A. T., a 9-month-old white female child, was sent to Vanderbilt University Hospital, March 18, 1957, for evaluation of her thyroid enlargement. At about 4 months of age she was found to be severely anemic and was started on oral iron. Hemoglobin at this time was 4 Gm. per 100 ml. Approximately 3 months prior to admission she was given 12 mg. of cobaltous chloride per day. The mother noticed a mass in the child's neck one week before admission and the child was referred to the hospital for evaluation by a local physician. Past history revealed no evidence of ingestion of a substance known to be goitrogenic other than the cobalt-containing compound. Examination revealed a thyroid which was diffusely enlarged and firm. It was estimated that the gland was 4 times normal size with a weight of 40 grams. No bruit was heard over the neck. The remainder of the physical examination was felt to be within the limits of normal.

Laboratory findings showed a hemoglobin of 10.2 Gm. per 100 ml. Cholesterol was 200 mg. per cent and the protein-bound iodine was 3.4 μg per cent (normal value in our laboratory 4 to 8 μg per cent). Films of the neck revealed a soft tissue mass in the anterior portion not displacing the trachea. Roentgenograms to determine the bone age showed carpal age slightly retarded with a suggestion of some delay in ossification.

The course of the patient in the hospital was unremarkable. It was recommended that the iron-cobalt containing medication be discontinued and that the patient be carefully followed after discharge. Six weeks later she was reported to have no evidence of thyroid enlargement by her local physician.

Case 3. N. P., a 21-month-old girl, was referred to the Vanderbilt Pediatric Service on July 23, 1960, with the chief complaint of "swelling in the neck." Ten months prior to admission she was noted to be anemic apparently on an iron deficiency basis. After receiving one transfusion, she was started on cobalt, 12 mg. per day initially, but later the dose was changed to 6 to 8 mg. per day. One month prior to admission she was noted to have an enlargement in the neck, and ½

grain of thyroid daily was prescribed. Despite the continuance of cobalt therapy, during the following 2 weeks the goiter apparently regressed. When the dose of thyroid was reduced to ¼ grain every other day and then after 2 weeks to ¼ grain every third day, the glandular enlargement reappeared but not to its original size. Review of the past history did not suggest that the child had received any other medication with known goitrogenic properties.

On physical examination the thyroid was firm and diffusely enlarged to approximately 3 times the normal size (Fig. 2). No nodules were palpated and no bruit could be heard.

Hemoglobin was 15.6 Gm. per 100 ml. White count was 10,400 with relative lymphocytosis. Cholesterol determination was 240 mg. per cent. Protein-bound iodine was 6.6 μg per 100 ml., and the 24-hour radioactive iodine uptake was 8.3 per cent.

Shortly after admission it was recognized that the child's condition was most likely that of thyroid hyperplasia induced by cobalt. The medication was discontinued. It was felt that other diagnostic procedures, such as biopsy, were unnecessary and the patient was discharged. She was seen again approximately 6 weeks later. Thyroid enlargement had completely subsided (Fig. 3), and the physical examination was entirely normal. At this time the hemoglobin level was 13 Gm. per 100 ml. Protein-bound iodine was 8.3 μg per 100 ml., and the radioactive iodine uptake for 24 hours was 18.6 per cent.

Fig. 3. Case 3. Regression of thyroid enlargement 6 weeks after discontinuation of cobalt.

Fig. 2. Case 3. Thyroid enlargement induced by cobalt.

DISCUSSION

The first suggestion that cobalt was goitrogenic was made by Gross, Kriss, and Spaet[7] who studied 4 children and one adult with sickle cell anemia in 3 of whom hyperplasia of the thyroid developed while the patients were receiving cobaltous chloride. One child became myxedematous and one had laboratory evidence suggestive of hypothyroidism. Commenting on the paper by

Dr. Gross, McBryde[7] reported giving an iron-cobalt preparation to 10 premature infants from 2 to 8 weeks of age. One of those being treated developed thyroid enlargement but 2 weeks after the cobalt was discontinued, glandular hyperplasia subsided. In a subsequent report by Kriss and colleagues[8] thyroid enlargement occurred in 4 children with anemia and one adult treated with cobalt. One patient developed myxedema and in 3 of them there was evidence of depressed thyroid function. The authors suggested that cobalt exerted its antithyroid effect by inhibition of one or more of the enzymatic reactions whereby thyroxine was formed from inorganic iodine. Following discontinuation of cobalt therapy, regression of the thyroid hyperplasia was noted.

Gross and associates[9] described the hematopoietic responses of children with anemia to cobaltous chloride and the thyroid dysfunction that resulted in 4 patients. If therapy with cobalt was continued longer than two months, the hematopoietic response dropped below pretreatment values as measured by the hemoglobin concentration. The children developed thyroid enlargement, and one became severely myxedematous. Hyperplasia disappeared upon discontinuation of the cobaltous chloride.

Lysaught[10] reported a case of goiter appearing during cobalt therapy in an infant receiving the medication for 4 months in doses of 80 mg. of cobaltous chloride per day. It was the author's contention that inhibition of activity was mediated through some of the enzymatic mechanisms of the thyroid, perhaps in the conversion of tyrosine to monoiodotyrosine. Gairdner, Marks, and Roscoe[11] studied the erythropoietic effect of cobalt on anemia in premature infants and observed one child who developed a large goiter after administration of 9 mg. of cobaltous chloride daily for 7 weeks. They cautioned against the addition of cobalt to iron preparations. The next report of the use of the same iron-cobalt preparation was by Weaver and co-workers[12] who observed thyroid enlargement during treatment of 8-month-old twins. The hyperplasia disappeared after discontinuation of iron-cobalt therapy.

Table I. Cobalt-induced thyroid hyperplasia —a summary of 22 cases

Source of data	*Date of report*	*Number of patients*
Gross et al.[7]	1954	3
McBryde[7]	1954	1
Gairdner et al.[11]	1954	1
Kriss et al.[8]	1955	5
Gross et al.[9]	1955	3
Lysaught[10]	1955	1
Weaver et al.[12]	1956	2
Robey et al.[13]	1956	1
Booth and Montgomery[14]	1956	1
Little and Sunico[15]	1958	1
Present report	1961	3

Within the past four years there have been 3 case reports of cobalt-induced thyroid dysfunction in the American literature. Robey, Veazey, and Crawford[13] described a case of a 17-month-old girl who was given an iron-cobalt preparation on the basis of 4 mg. per kilogram of body weight for 12 weeks. The thyroid was diffusely enlarged, hard, smooth, and nontender. Clinical and laboratory evidence of myxedema was present. Because of her precarious cardiac status she was started on thyroid therapy. There was marked improvement. Booth and Montgomery[14] observed enlargement of the thyroid in a 4-month-old white male who had been started on 40 mg. of cobaltous chloride and 75 mg. of ferrous sulfate daily while in the premature nursery. He was readmitted to the hospital with a history of episodic apnea and cyanosis. Laryngoscopy revealed edema of the laryngeal mucous membrane; the right vocal cord was thought to be paralyzed. Thyroid enlargement was first noted while the child was under anesthesia. Difficulty with secretions necessitated tracheotomy, at which time considerable inflammatory tissue was observed between the trachea and thyroid. The infant's death was attributed to obstruction of the airway by excessive mucous. The findings in this case have many similarities to those in one of our cases (Case 1). Finally, cobalt has been in-

criminated by Little and Sunico.[15] They found a 6-month-old infant who had received 40 mg. of cobaltous chloride daily for 90 days. The thyroid enlargement was of such severity that the child became cyanotic during a technical procedure. The infant responded well to digitalization. Radioactive iodine uptake studies showed no evidence of myxedema; a protein-bound iodine value was not obtained. Five weeks after discharge the thyroid was not palpable. Table I summarizes cases of thyroid enlargement presumably caused by cobalt.

Thyroid enlargement was felt to be related to cobaltous chloride administration in 5 of 10 cases studied by Klinck[16] at the Armed Forces Institute of Pathology during a two-year period. He stated that thyroid hyperplasia was of such severity that a diagnosis of adenocarcinoma was considered. Histologically, follicles were for the most part obliterated and only occasionally did some of the acini reveal intraluminal collections which were interpreted to be colloid. Mitotic activity was not evident in most of the sections studied. On a histologic basis it was impossible to distinguish patients who had received cobalt from those who had not.

Contradictory evidence of the goitrogenic property of cobalt was presented by Jaimet and Thode[17] in their studies of thyroid function in children receiving cobalt therapy. They administered the medication in doses providing 1, 2, 4, and 6 mg. of cobaltous chloride per kilogram of body weight daily for 10 weeks without evidence of thyroid dysfunction and concluded that cobalt did not affect the gland in vivo. Their conclusions were questioned by Kriss and associates.[18] The dose of cobalt was generally below that which had been used by Kriss. Three patients who did receive high doses showed reduction of thyroid function. Kriss felt that it was unwarranted for the authors to disregard these subjects after a second course of cobalt therapy did not result in depressed function.

Experimental evidence in animals of the goitrogenic action of cobaltous chloride was reported by Antila and co-authors.[19] Cobalt was administered to guinea pigs by intraperitoneal injection. The authors found that doses of 8 mg. per kilogram of body weight had goitrogenic properties, whereas, 2 mg. per kilogram seemed insufficient to cause thyroid hyperplasia which could be recognized histologically. That cobalt has a definite effect on chick thyroid function seems valid from the studies of Kriss and associates.[20] The drug was found to decrease radioactive iodine uptake, increase the uptake of radioactive phosphorus, and to cause no colloid depletion. The conclusions reached by the authors was that cobalt probably has a direct effect upon the thyroid cell with inhibition of endocrine function and promotion of phosphorus uptake.

The explanation as to why certain individuals develop thyroid enlargement when treated with cobalt and others do not has been recently investigated by Paley, Sobel, and Yalow.[21] The authors studied the effects of intravenous and oral administration of cobaltous chloride on euthyroid and hyperthyroid patients. Cobalt inhibited thyroid binding of radioactive iodine as demonstrated by the discharge of I^{131} from the thyroid with sodium thiocyanate. Approximately one half of the subjects showed depressed I^{131} uptake, and it was concluded that higher doses of cobaltous chloride would have resulted in complete depression. If gastrointestinal absorption, dosage of cobalt, and duration of therapy are not the sole determinants of thyroid hyperplasia, it is interesting to speculate that individual susceptibility may be related to a specific inheritable defect at the enzymatic level in the conversion of inorganic iodine to thyroxine.

SUMMARY

Three cases of thyroid enlargement presumably induced by an iron-cobalt preparation are presented. One case demonstrated hyperplasia at autopsy and 2 had enlargement of the gland that regressed upon discontinuation of the medication. The probable relation between cobalt and the appearance of goiter is discussed. A warning is voiced against the use of cobalt in the treatment of anemia.

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Should infantile umbilical hernias be treated with navel emplastra?

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UMBILICAL hernias in infants occur when the locus minoris resistentiae, commonly present in the upper part of the umbilical ring, cannot withstand the pressure in the abdominal cavity, with the result that a portion of the intestine is pressed into a hernial sac. These herniations are so common in infants during the first months of life that one is tempted to refer to them as being to some extent physiologic. Riisfeldt,[1] for instance, reported from the Rigshospitalet in Copenhagen that no less than 24.7 per cent of the infants in his study had umbilical hernias during the first month of life; at 3 and 12 months of age the figures were 24.5 per cent and 11.5 per cent, respectively. This decrease in frequency has also been mentioned by Watson[2] and Scharff,[3] and other investigators.[4, 5] In most instances, umbilical hernias show a similar tendency to regression after the age of infancy. Riisfeldt[1] noted in a series of school children that the incidence of hernias was 4.03 per cent among children 7 years of age and only 0.25 per cent among those of 14 years. Hence, judging by these figures, there is a decrease in frequency from 24.7 per cent to 0.25 per cent between the first month of life and adolescence. This decrease suggests that a conservative attitude should be adopted with respect to treatment. The following conditions should, in my opinion, form the main indications for operation of umbilical hernias in children under 14 years of age: (1) irreducible or incarcerated hernia (rare), (2) a large hernia, and (3) a hernia showing a definite tendency toward an increase in size.

According to the commonly used pediatric and surgical textbooks umbilical hernia in infants should be treated by the application of an emplastrum. Some workers recommend the use of a pad over the navel; others consider this to be inadvisable. Some apply the plaster as far as the posterior axillary line or the flanks; others continue it around the whole body. The theoretical reasoning underlying plaster treatment is that the plaster will resist the intra-abdominal pressure and hold the protruded part in position until the connective tissue in the umbilical ring has gained sufficient stability to withstand the pressure in the abdominal cavity. It would, however, be interesting to know the course of events with hernias that are not treated. Do they show a lesser tendency to heal than those treated with plasters? I have not found any reports on this subject, and all statements on the excellence of plaster treatment

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Table I

Subgroups by size of hernia and total group	*Treated*		*Nontreated*		*Total*
	No.	*% of total*	*No.*	*% of total*	*No.*
I	34	40.5	50	59.5	84
II & III	22	55.0	18	45.0	40
All cases	56	45.2	68	54.8	124

seem to be based on purely subjective opinions, or else its recommendation is merely a matter of tradition. The present investigation was carried out to throw light on the problem.

For the past 2½ years I have treated alternate cases of infantile umbilical hernia at the Karlstad Child Welfare Centre with plasters; the others received no treatment. The plaster was applied in the manner usually employed in Sweden, the hernia being restored and the skin drawn tightly together into a longitudinal fold over the umbilical ring and held in this position with an approximately 5 cm. wide elastic plaster band, which extended as far as the axillary lines. The treatment was not begun before the infant had reached the age of 1 month; as a rule the age at application was 1 to 2 months. The plaster was renewed before it fell off or when it had begun to loosen at the edges, the exchange being carried out either by myself, when the mothers visited the Centre, or by the nurses during their home visits. Only when the skin was extremely irritated by the plaster was it allowed to "rest" for a few days before a new plaster was applied. The treatment was continued until the hernia had disappeared or until the infant was 1 year of age.

During the 2½ years of the study, 1,526 infants were registered at the Karlstad Child Welfare Centre, and 170 (11.1 per cent) had umbilical hernias. Among these, 89 (52.4 per cent) were boys and 81 (47.6 per cent) were girls; thus, no appreciable differences in sex distribution could be established, the deviation from 50 per cent lying well within the limit of the standard error, which is ± 3.8 per cent. Eighteen (10.6 per cent) of the 170 infants had a birth weight of less than 2,500 grams. According to Riisfeldt,[1] the lower the birth weight the greater is the disposition to umbilical hernia.

The infants were classified into groups according to the size of the hernia and, more importantly, the size of the orifice. Those with small hernias were placed in Group I, those with a medium-sized orifice permitting the passage of a finger tip in Group II, and those with a larger opening in Group III. Although this classification was to a large extent subjective it resulted in 84 cases being placed in Group I, 32 in Group II, and 8 in Group III.

In one instance in which the hernia had disappeared when the infant was 5 months old, it returned again at 15 months of age, and in another it had increased in size. In all other cases in which the condition had healed the size of the hernia had gradually decreased.

When the material was analyzed with respect to disappearance of the hernia, 46 of the 170 infants were eliminated, either because healing had not taken place at the time of the investigation or because they had not been kept under sufficiently strict observation. Hence, 124 cases remained for

Table II. Percentages of healed umbilical hernia at several ages

	*Treated**			*Nontreated*		
	Before 4 months	*Before 6 months*	*Before 12 months*	*Before 4 months*	*Before 6 months*	*Before 12 months*
Group	*P ± ε (P)*†	*P ± ε (P)*	*P ± ε (P)*	*P ± ε (P)*	*P ± ε (P)*	*P ± ε (P)*
I	52.9 ±‡ 8.6	88.2 ± 5.5	100.0	58.3 ± 7.0	86.0 ± 4.9	100.0
II + III	36.4 ± 10.3	68.2 ± 9.9	86.4 ± 7.3	11.1 ± 7.4	55.6 ± 11.7	72.2 ± 10.6
Total	46.4 ± 6.7	80.4 ± 5.3	94.6 ± 3.0	45.6 ± 6.0	77.9 ± 5.0	92.6 ± 3.2

*Hernias were usually "strapped" when the infant was between 1 and 2 months of age.

†P ± ε (P) = percentage.

‡± standard error of percentage.

analysis, and of these, 56 had received plaster treatment and 68 had not been treated for their hernia. Actually, the two series should then constitute exactly one half. The standard error of 50 per cent, applied to 124 cases, is 4.5 per cent, and the deviation of 45.2 per cent and 54.8 per cent, respectively, falls well within the limit of the standard error.

Table I shows the material classified in the different groups. It will be noted that among the treated infants the milder cases were slightly underrepresented and the more severe cases, i.e., Groups II and III, slightly overrepresented. The displacement is, however, not greater than what may be expected to be due to chance. Because of this distribution, the result may be expected to be slightly worse in the treated than in the nontreated cases.

It will be seen, however, that there is no statistically significant difference between the groups (Table II). For infants under 4 months of age, the incidence of healing was 46.4 per cent in the treated group and 45.6 per cent in the nontreated one. The difference is much less than the standard error, namely 0.8 ± 9.0 per cent. The same features are to be noted after 6 months, when healing was established in 80.4 per cent of the treated cases and in 77.9 per cent of those not given treatment. The difference is 2.5 ± 7.3 per cent. After 12 months healing occurred in 94.6 per cent of the treated group and in 92.6 per cent of the nontreated one. The difference is inconsiderable, when compared with the standard error (2.0 ± 4.4 per cent). Similar comparisons of the subgroups also show good agreement.

SUMMARY

Among 124 infants with either small or medium-sized umbilical hernias the condition healed in most instances (95 per cent) within one year. Approximately one half of the patients were treated with a navel plaster, while the other half received no treatment. No difference in the healing tendency of the hernias between the treated and nontreated groups could be established; hence the investigation strongly suggests that plaster treatment is not necessary in the case of small and moderately large umbilical hernia.

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A case of hypersensitivity to para-aminosalicylic acid in a child

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THE extensive use of para-aminosalicylic acid since 1948 in the treatment of tuberculosis has resulted in an increasing number of reports of hypersensitivity to this drug.

It was felt of interest to report a case in a small child, which demonstrated features now considered characteristic of this condition.

CASE REPORT

A. T., a female child, aged 4 years, was admitted to the Adelaide Children's Hospital on May 17, 1960. Both the patient and a sibling had developed positive Mantoux reactions following contact with an uncle who had been found to have active pulmonary tuberculosis.

The chest x-ray of the child revealed opacities "consistent with active pulmonary lesions"; gastric washings were collected and therapy was begun on May 20 with streptomycin 500 mg. daily, isoniazid 200 mg., and para-aminosalicylic acid 6 Gm. daily.

In vitro sensitivity tests on June 7 revealed only weak susceptibility to isoniazid, so this drug was discontinued.

The child remained clinically well until June 16, the twenty-eighth day of therapy, when a maculopapular rash developed on the trunk and limbs, and the temperature rose to 101° F. Measles was provisionally diagnosed; however, on June 17, cervical lymphadenopathy developed and the pyrexia increased the following day to 104° F. (see Fig. 1). No change was noted until June 21, when generalized lymphadenopathy occurred.

On June 24, the possibility of a "drug reaction" was considered and streptomycin was discontinued. At this stage slight enlargement of the liver and of the spleen was noticed. A day later the enlargement of these organs had increased markedly, and the lymphatic enlargement was much more prominent. Urinalysis showed an excess of urobilinogen.

A rapidly progressive reticuloendotheliosis, possibly Letterer-Siwe disease, appeared a likely diagnosis and skin and lymph node biopsies were taken.

On June 30, sensitivity to para-aminosalicylic acid was first considered and therapy with this drug was discontinued. Within 4 days the hepatosplenomegaly regressed, and the child improved clinically. Twelve days later these organs had returned to normal size, and she had returned to her usual good humor.

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To confirm the diagnosis, administration of the drug was again instituted on July 16 in increasing dosage, 6 days later splenomegaly and lymphadenopathy returned; however, she remained fever free. Following final discontinuance, she returned to normal within several days.

Investigations. Gastric washings and guinea pig inoculations were both positive for tubercle bacilli.

Routine serum agglutination tests (including the Paul-Bunnell), blood cultures, fecal and urine cultures, cerebrospinal fluid examination, and L.E. cell studies were all negative.

Skull x-ray (to exclude bone lesions associated with reticuloendotheliosis) was normal. Bone marrow examination and culture were normal. Fetal hemoglobin was 1.5 Gm. per cent, and C-reactive protein was normal.

Skin and lymph node biopsies revealed "nonspecific inflammatory changes."

Serum glutamic pyruvate transaminase on June 27 was 230 units (normal 5 to 35 units). Hepatic function tests included: thymol turbidity, 2 units; zinc sulfate, 3 units; and serum alkaline phosphatase, 17 K.A. units. Blood data are listed in Table I.

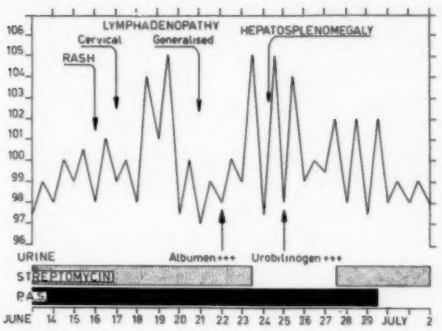

Fig. 1.

DISCUSSION

The features of this case are characteristic of those found in previous reports of para-aminosalicylic acid hypersensitivity.

Friedmann[1] in 1955 reviewed the diversity of modes of presentation reported in the literature of cases of this nature which included neuropsychiatric features simulating the Guillin-Barré syndrome, encephalopathy, or a schizophrenic state. It may also become manifest by hematologic disturbances with a peripheral blood picture showing leukemoid features or leukopenia, or frequently a transient eosinophilia. Several cases have been recorded in which the peripheral blood showed an excess of atypical lymphocytes and caused confusion with glandular fever.

Hypersensitivity also has been manifest by pulmonary signs suggesting allergic pneumonitis, particularly when accompanied by eosinophilia. Clinical and histologic evidence of hepatitis was also found in patients who developed jaundice or hepatomegaly as a manifestation of para-aminosalicylic acid hypersensitivity.

The protean character of the disturbances attributed to this situation is likely to cause confusion in the clinical diagnosis of such symptoms occurring during para-aminosalicylic acid therapy. However, fortunately, the incidence of hypersensitivity reactions is low. Cannemeyer, Thompson, and Lichtenstein[2] in 1955 reported 14 cases in 5,000 patients receiving the drug, an incidence of 0.3 per cent.

In this child symptoms became apparent on the twenty-eighth day of therapy; in

Table I

Date	*Hemoglobin (Gm./100 ml.)*	*Leukocyte count*				
		Total	*Polymorphonuclear leukocytes*	*Lymphocytes*	*Monocytes*	*Eosinophils*
May 19, 1960	11.0	10,500	65	28	3	4
June 20, 1960	10.6	4,100	57	34	6	3
June 27, 1960	9.3	15,000	45	38	10	7
July 4, 1960	10.2	10,800	17	78	4	-

previous reports Dixon[3] in 1954 stated the range of onset of symptoms to be from the twenty-second to the forty-sixth day after commencement of therapy. The onset was acute in our patient with pyrexia, a rash, and signs of general ill health which included nausea, vomiting, hepatosplenomegaly, and lymphadenopathy as described by Cuthbert[4] and by Lichtenstein and Cannemeyer.[5] The hepatic and splenic enlargement was not apparent until 9 days after the onset of symptoms. The rash, typically maculopapular or scarlatiniform, as described by Hensler, Singer, and Hill,[6] was a prominent feature.

Hepatic involvement was evidenced by excessive urinary urobilinogen excretion, rapid hepatic enlargement, and a grossly elevated serum glutamic pyruvate transaminase despite the lack of other abnormal liver function tests or of clinical jaundice. Cholangiolitic hepatitis was present in a case observed by Hensler, Singer, and Hill.[6] Hepatitis of this type has proved to be the most serious effect of para-aminosalicylic acid hypersensitivity; 6 fatal cases have been reported by Lichtenstein and Cannemeyer.[5] It is of interest that only 2 of their 14 cases had clinical evidence of jaundice.

Confirmation of the diagnosis was made by the reproduction of symptoms and signs following readministration of the drug several weeks later. Extreme caution is advocated by Davin and Rogers,[7] if a second course of therapy is contemplated. Desensitization has been suggested by Steel[8] if it is thought necessary to continue therapy with this drug.

However, in patients exhibiting evidence of para-aminosalicylic acid hypersensitivity, particularly if associated with evidence of hepatic involvement, discontinuance of its administration or substitution of other therapy would appear to be indicated.

SUMMARY

The case of a child exhibiting clinical evidence of para-aminosalicylic acid hypersensitivity is reported. The difficulty in diagnosis of this condition due to the variety of clinical patterns is briefly discussed. Awareness that hypersensitivity to this drug may exist in a child who develops pyrexia and a rash during antituberculosis therapy is mentioned so that similar cases may be diagnosed before hepatic involvement becomes manifest.

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Phenylketonuria. I. Dietary management of infants and young children

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SINCE the recognition of phenylketonuria in 1934,[1] there have been many attempts to cure or prevent the mental deficiency associated with this disease. The first significant improvement came with the institution of low phenylalanine diets during the early 1950's.[2-4] Soon after, it was demonstrated that early initiation of the special diet in infancy could prevent the mental deficiency of phenylketonuria.[5, 6]

We have had an opportunity during the past 3 years to treat a group of infants and young children with a new low phenylalanine food, Lofenalac.† The diets of the first 10 children who were treated have been analyzed and form the basis for this report. The uniformly good acceptance of this food has led to a simple plan of management. Except for one institutionalized child, all the children in this report were placed on the diet as outpatients in their own homes. No child required hospital management while on the new food, and none have had to be taken off the diet. Contrary to the marked difficulties and complications associated with diets in some of the earlier studies,[7, 8] we have found it relatively easy to maintain children on this new diet.

In this paper the general method of studying and managing children with phenylketonuria is discussed and a simple plan for the diet outlined. Analysis of various components of the diet as required by these children is also presented. In a companion article the results of treatment (including mental development and physical growth) are described in detail.[9]

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SELECTION OF CHILDREN FOR DIETARY TREATMENT

It is generally accepted that the earlier treatment is begun, the better the results will be.[6] However, there is uncertainty as to the age after which the extent of improvement to be expected would be so slight that trial of treatment would not be justified. A review of the results of treatment shows little evidence of significant improvement

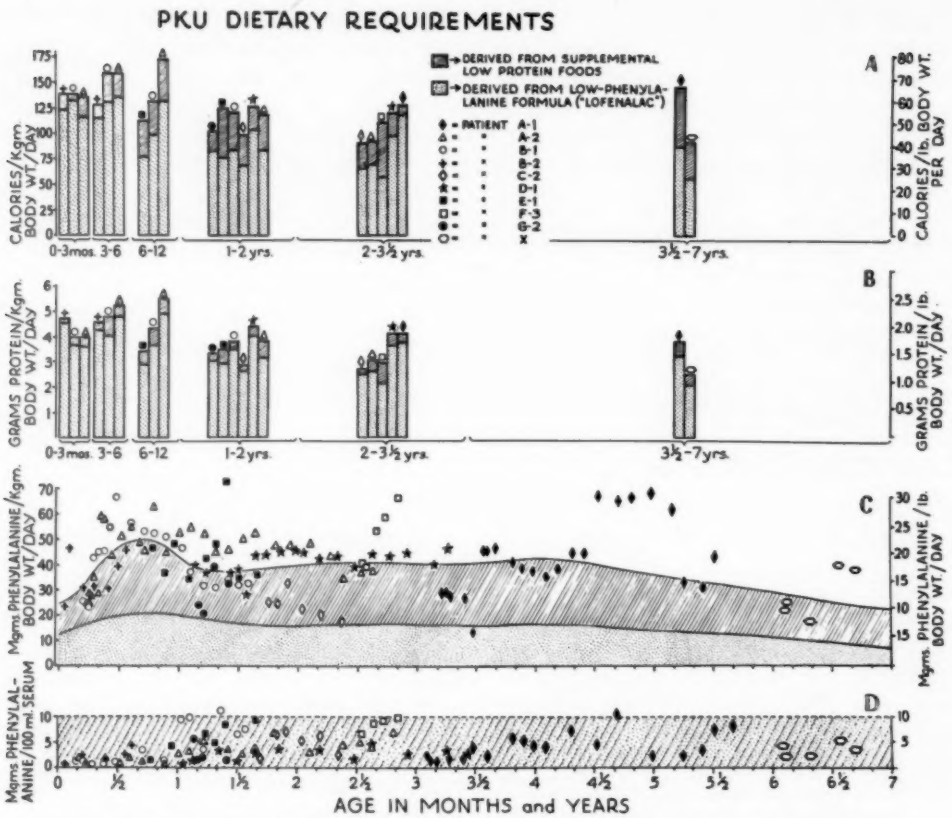

Fig. 1. Daily dietary intakes of 10 children with phenylketonuria on low phenylalanine diets, given as averages for various age periods, correlated with the serum phenylalanine levels. Each letter (A through X) represents a different family. The oldest child with phenylketonuria in the family is given No. 1, the next oldest, No. 2, etc. Patient X is the one institutionalized child.

in the I.Q. when the diet was initiated after 3 years of age[6] although such delayed treatment frequently does result in improvement of irritable behavior patterns, abnormal electroencephalograms, convulsions, and eczema.[2, 4, 6] On the other hand there are instances of significant mental improvement due to treatment after the age of 3 years and of significant regression due to the untreated disease after this age.[10-12, 15] Woolf and colleagues[13] have expressed the opinion that treatment may be responsible for significant improvement in the 2-year-old with an I.Q. of 20 or above, the 3-year-old with an I.Q. of 30 or above, the 4-year-old with an I.Q. of 40 or above, and the 5-year-old with an I.Q. of 50 or above. He would prescribe dietary treatment for all children under 2 years of age with phenylketonuria.

In general, we have treated all children under 3 years of age. A child with moderate mental retardation (I.Q. above 30) between the ages of 3 and 5 years probably should have also a trial of treatment, other factors such as availability of the diet and parent cooperation being favorable.

DIETARY REQUIREMENTS

The protein in natural foods contains about 5 per cent phenylalanine.[14] It is impossible, therefore, to devise a diet from natural food that is markedly low in phenylalanine without being deficient in protein.

In the diet described here, approximately

80 to 90 per cent of the protein requirement in provided by a synthetic, low phenylalanine formula, Lofenalac (Fig. 1, *B*). This is a powder which contains a mixture of amino acids plus fats and carbohydrates to make a balanced formula which can be dissolved in water to make a milk substitute. If Lofenalac were the only source of protein, the diet would be deficient in phenylalanine, the serum level would become subnormal, and there would then be such evidences of phenylalanine deficiency as growth retardation, catabolism of body proteins, and a paradoxical rise in the serum phenylalanine level.

Fig. 1, *D* shows 93 determinations of the serum levels of phenylalanine of the 10 children while on the diet. Ninety-one (97.8 per cent) of these were below 10 mg. per 100 ml.; 83 (89.2 per cent) were below 8 mg. per 100 ml. Only 6 (6.5 per cent) were below 1 mg. per 100 ml., which is considered to be the lower limit of normal. Subsequent observations for 6 months of 9 of these patients and of another infant (these data are described in the companion article) revealed that 114 of 121 serum levels (94.2 per cent) remained under 10 mg. per 100 ml. and 101 (83.5 per cent) remained under 8 mg. per 100 ml. It was felt that the children did well with levels up to 8 mg., and that children with levels below 3 mg. for a prolonged time did not appear to do any better than when their diets were liberalized a little. Symptoms such as irritability and poor sleep usually did not appear until serum levels were above 10 mg. per cent. However, pending further observations, it is suggested that an effort should be made to maintain the serum phenylalanine level between 2 and 6 mg. per 100 ml. Perhaps during the crucial first year of life, a 2 to 4 mg. per 100 ml. range should be the goal. There is lack of consensus, however, as to what should be considered the safe range; some would say that our suggested ranges are too liberal[15] and others that they are not liberal enough.[16]

The intake of phenylalanine was determined by the level of serum phenylalanine which was desired; this is illustrated by curves *C* and *D* of Fig. 1. For infants under 3 months of age the diet was carefully restricted, and the serum level was kept below 3 mg. per 100 ml. of serum. It was soon discovered that these small infants could tolerate two or more times this amount of phenylalanine in the diet without raising the serum phenylalanine level above 5 mg. per 100 ml. We believe that the infant under 3 months can tolerate 20 mg. or more per pound per day of phenylalanine; however, it is very easy to give a more restricted diet at this age. After 1 year of age there seemed to be less ability to utilize phenylalanine, and the intake, which varied considerably between individuals, was decreased to amounts varying from 20 to 10 mg. per pound per day; with these intakes the serum phenylalanine varied between 2 and 8 mg. per 100 ml. The stippled portion of graph *C* shows that 30 to 50 per cent of the phenylalanine is provided by Lofenalac, the remainder by natural foods.

The caloric intake of the children is of interest. In Fig. 1, *A* the average daily intakes are plotted according to the age of the child. The daily consumption of 40 to 80 calories per pound of body weight per day, depending on the age and size of the child, was consistently higher than that considered necessary in a natural diet for normal children. Sixty to 80 per cent of the calories was provided by Lofenalac. The protein equivalent intake was above the recommended daily requirement of about 1½ Gm. per pound of body weight per day (Fig. 1, *B*). In later cases we have prescribed a little less Lofenalac; the response has been as satisfactory. The dietary suggestions in Table I reflect our present thinking in regard to the needs of these children and may differ a little from the values on the graphs.

METHOD FOR CALCULATING LOW PHENYLALANINE DIETS

The outlines in Tables I and II have been prepared to emphasize the basic simplicity of this diet. Table I gives a method for cal-

Table I. Daily low phenylalanine* diet for infants and young children

Age group and approximate basic requirements† (suggested serum PA level for all age groups: 2 to 6 mg./100 ml.)	*Lofenalac basic source of protein (1 measure = 1 Tbsp.)*	*Milk used to raise PA level*	*Primary foods‡ (low in PA) All fruits Common vegetables except potatoes, corn, and legumes§*	*Secondary foods‡ (moderate PA values) Breads Cereals Cookies Potatoes Corn*	*Free foods‡ (no significant PA) Hard candies Jellies and honey Sugar and syrup Cornstarch and tapioca Oils*	*Foods to avoid‡ (high in PA) Meat, poultry and fish Eggs, cheese Nuts, peanut butter Legumes§*
Birth to 3 months 60 to 65 Cal./lb. 20 to 22 mg. PA/lb.	1¼ to 1½ Tbsp./lb.	⅛ oz./lb.	0	0	0	0
3 to 12 months 55 to 60 Cal./lb. 18 to 20 mg. PA/lb.	1 to 1¼ Tbsp./lb.	1/10 oz./lb.	½ oz.‖/lb.	0	0	0
1 to 3 years 50 to 55 Cal./lb. 16 to 18 mg. PA/lb.	¾ to 1 Tbsp./lb.	0 to 1/20 oz./lb.	⅔ oz.‖/lb.	2 small servings	Small amounts for treats and desserts (too much may dull appetite)	0
3 to 7 years 40 to 50 Cal./lb. 10 to 16 mg. PA/lb.	½ to ¾ Tbsp./lb.	0	⅔ to ¾ oz.‖/lb.	2 to 3 moderate servings	Usually liberally	0

*PA, phenylalanine.

†Including supplementary vitamins daily and iron as indicated.

‡For complete diet lists refer to—Acosta, P.B., and Centerwall, W. R.,[18] Primary foods, Lists II and III; Secondary foods, List IV; Free foods, List VII; and Foods to avoid, List VIII.

§Legumes include peas and beans (except stringbeans).

‖1 oz. by measure = 2 tablespoons.

culating proper amounts of Lofenalac and supplementary foods for various age groups. Table II shows samples of menus prescribed from this diet outline. The diet so prescribed usually will reduce the serum phenylalanine to the suggested level of 2 to 6 mg. per 100 ml. Small adjustments in the diet should be based on the levels obtained. All of the children were given daily supplementary vitamins (0.6 c.c. of Deca-Vi-Sol) and iron (0.6 c.c. of Fer-In-Sol).

One measure of Lofenalac powder in 2 oz. of water makes a 20 calorie per ounce formula resembling milk. This formula is satisfactory for infants when supplemented with a small quantity of milk. Infants and small children can be started on the formula without supplements in order to bring serum phenylalanine levels down more rapidly. The decrease to the normal range usually occurs in a week or two. About a month may be required to establish a dietary program, including the formula and supplements, on which a satisfactorily low serum phenylalanine level may be maintained.

Since most of the dietary calories as well as protein come from Lofenalac it is important that the child take an adequate amount of it daily; there is then less craving for other foods which necessarily must be limited. Most small children like Lofenalac as a beverage; some prefer to eat it mixed

in their supplementary foods. As the baby grows, it seems desirable to increase gradually the concentration of the formula so that adequate amounts of protein equivalent can be ingested without an excess fluid load (see sample menus in Table II).

In the diet outlines (Tables I and II), it can be seen that the need for extra phenylalanine is met by giving a selection of foods which are low in protein. The use of low protein supplements has the advantage of providing as large a quantity and variety of natural foods as possible. With experience, mothers may want to try increasing the variety of foods. Early in the study of these diets, Lyman[17] prepared diet lists which give equivalent portions of various foods. One "equivalent" of food was that portion supplying 15 mg. of phenylalanine. These lists and others[18] based on the same principle make it easier for the mother to vary the diet without exceeding the prescribed amount of phenylalanine. Special recipes also are available for this purpose.[17, 18] We feel, however, that *good control is most satisfactorily attained when fruits and vegetables (primary foods of Table I) are the principal source of supplementary foods.* Excess amounts of the other foods can easily result in loss of dietary control.

The dietary plan is based on a protein requirement of approximately 1½ Gm. per pound of body weight per day for infants and slightly less for young children above 1 year of age. Because Lofenalac contains about 1½ Gm. of protein equivalent per measure, it is an approximate rule that infants require 1 measure per pound per day. One measure of Lofenalac contains 7.5 mg. of phenylalanine. Because average total phenylalanine needs are about 18 mg. per pound per day (see Table I and Fig. 1, *C*), about 10 mg. per pound per day must be provided by other food. Requirements vary somewhat from child to child.

MANAGEMENT OF THE CHILD ON A LOW PHENYLALANINE DIET

Because of difficulties with unpalatable diet mixtures which were used initially in the dietary treatment of phenylketonuria, it is generally believed that low phenylalanine diet management is fraught with hazards to the child's physical and psychological health as well as adverse effects on the family. In our experience with Lofenalac there has been almost a complete absence of any of these problems. We believe that it is the simplicity of our basic dietary plan, Lofenalac plus common fruits and vegetables, that has made this possible. Any physician who is able to spend a little extra time with the family at the start can supervise this diet. The following discussion is intended to show how this has been done in our clinic on an outpatient basis.

The 10 children in this report have been under diet control from 6 months to 2¾ years (average of 16 months per child). Three of the children were started on the diet at under 2 months of age,* one at 8 months, five at from 1 to 3 years, and one (an institutionalized child) at 6 years.†

All of the children, except the one institutionalized child, were referred to us for management immediately after the diagnosis was made. Because of the degenerative nature of the disease, an effort was made to start the diet without delay. A secondary gain derived from prompt initiation of the diet was that the parents were impressed at once with the importance of the diet to their child.

For each child, a detailed history, physical examination, psychometric evaluation, photographs and motion pictures, laboratory tests, including a serum phenylalanine determination,[19] and an electroencephalogram, were obtained. The parents were counseled

*Since the preparation of data in Fig. 1, *A, B, C,* and *D,* an additional newborn infant (*H-2*) has been under our care. Her diet has been prescribed in accordance with the plan outlined in this article; and after 6 months, results (except for several months of generalized rash) have been good, and comparable to those observed in our other young infants.

†We are indebted to the staff at Pacific State Hospital, California, for the cooperation which made study of this child (Case X) possible. She was chosen for treatment specifically to study the diet requirements in a slightly older child. She was very retarded and no increase in I.Q. was expected. She did show brightening of affect which has been previously described in older patients on the diet.[2, 6]

in detail concerning the disease, dietary requirements were explained, and literature was provided.[20] The special food product, Lofenalac, was provided and the child was started immediately on the diet, usually initially with the Lofenalac formula alone. After an interval of one week, usually, parents and child were seen again. At this visit, parents had many questions to ask, and often needed reassurance about the diet. At this time also a second blood specimen was taken for a phenylalanine determination and, except with small infants, selected low protein solid foods were started.

The child was seen again in two weeks, or more often if necessary, and then at monthly and eventually bimonthly intervals. Serum phenylalanine levels were taken frequently (every visit or every other visit) and the urine was checked for phenylpyruvic acid at each visit. The ferric chloride urine test alone is not a good indicator because the urine remains negative with such a test until the serum phenylalanine reaches about 12 mg. per 100 ml. In addition, for research purposes, occasional hemoglobin determinations and infrequent serum protein levels were obtained; each child had repeat photographs, electroencephalograms, and developmental studies at approximately 6 months' intervals.

We agree with Umbarger[21] about the disadvantages of hospitalization. All of our children were started on the diet at home and none have required hospitalization because of the Lofenalac diet. There were no significant periods of weight loss or lack of phenylalanine control. Although the phenylalanine serum levels were brought down rapidly, there were no untoward reactions. Blood hemoglobin and total serum protein levels remained within the normal range.

There were, of course, minor problems that arose in the course of treatment. The initiation of the milk substitute formula itself was usually quite uneventful. For instance, no flavorings have been used. A firm positive attitude that the child would get used to the formula in a few days was all that was needed in most instances. One family which could not return for a month after the first visit followed the alternative suggestion of adding the powdered formula to other foods; there were no apparent difficulties. Slight problems were experienced in homes with several older siblings. In this situation it is apparently difficult for the mother to keep extra food, especially cookies and crackers, away from the child under treatment. These children took the formula well but still had a healthy appetite for "goodies," and the mother had to be very vigilant.

All initial orientation and dietary management were done by a pediatrician (W. R. C.). In presenting the diet we assumed the same attitude and role as any other physician who instructs the mother in dietary management of the young baby. We avoided having the mother concerned about calculations of protein or phenylalanine or weighing or measuring the food. If the child was an infant, the Lofenalac was described as a new formula. If a young child was involved, it was called a milk substitute. The mother was instructed how to mix the formula and how much to give each day. She was also told approximately how much of the fruits and vegetables her child could have. The latter was usually about equal to what the child would desire when he was taking the prescribed Lofenalac. Pressure for consumption of exact amounts of food or formula was avoided at first and subsequently has proved to be unnecessary. However, the mother was advised that as soon as her child became accustomed to the new formula, approximately the prescribed amount should be taken each day. On later visits the amounts of supplementary foods were varied as indicated by serum phenylalanine level. If not enough fruits and vegetables were being taken to keep the level above 2 mg., a little milk was added to the formula and/or some "secondary foods" were given (Table I).

The dietitian has been an able assistant in devising recipes and in helping the mother to vary the diet. This type of counseling was a part of the continuing program, but we found that it was better to limit supplementary foods to fruits and vegetables until the

Table II. Sample low phenylalanine menus*

Age and weight	*Formula*	*Breakfast*	*Mid-morning*	*Dinner*	*Mid-afternoon*	*Supper*
1 month (8 pounds)	12 measures Lofenalac 1½ oz. milk 24 oz. water	Six or seven 3 to 4 oz. feedings of formula plus supplementary vitamins				
6 months (15 pounds)	19 measures Lofenalac 1½ oz. milk 26 oz. water	5 tablespoons applesauce 8 oz. formula Supplementary vitamins and iron		5 Tbsp. puréed carrots 8 oz. formula		5 Tbsp. puréed peaches 8 oz. formula (also 8 oz. formula at bedtime)
18 months (23 pounds)	23 measures Lofenalac 1 oz. milk 18 oz. water	2 tablespoons precooked rice cereal with 2 oz. formula and sugar 1½ canned peach halves 6 oz. formula Vitamins and iron	1 small apple	½ cup cooked carrots 2½ tablespoons mashed potato made with butter or formula but no milk 6 oz. formula	2 animal cookies 4 oz. formula	3 tablespoons green beans 3 canned pear halves 6 oz. formula
4 years (36 pounds)	27 measures Lofenalac 25 oz. water	½ cup Puffed Rice with 3 oz. formula and sugar ¾ cup orange sections 8 oz. formula Vitamins and iron		½ cup cooked carrots ¼ medium cucumber sliced 5 tablespoons mashed potato made with 1 tsp. butter and some formula ½ cup applesauce 8 oz. formula	½ fresh peach 4 oz. formula	6 tablespoons cooked green beans 3 canned pear halves 3 animal cookies 8 oz. formula

*Foods from special diet lists and special recipes may be substituted.[34, 35]

diet was well regulated. By this time the mother had an appreciation of the value of the diet. She knew her child was eating well and doing well. Most parents were satisfactory dietary managers, and it became increasingly clear that a simple dietary plan could be formulated.

Since phenylalanine equivalent lists and special recipes are now available,[17, 18] the average physician has all the aids he needs for supervising the diet with the exception of a laboratory for serum phenylalanine determinations. This service is now available at many medical centers and some laboratories.

The difficulties described by other investigators[7, 8] with the dietary control of children with phenylketonuria are well known to us. The first 3 children in our series were started for a few months on another casein hydrolysate product, Ketonil* (see Charts *A-1, A-2,* and *B-1* in the companion article[9]). The oldest child *(A-1)* was very resistant to this preparation and lost weight so rapidly that he required hospitalization. The only way his mother could make him swallow the formula was by sheet wrapping and forced feeding. When he was changed to Lofenalac, he took it readily and thrived. The 2 small babies (A-2, B-1), who were also given the other food at first, took it well but they did not show as good a weight gain as they did later on Lofenalac.

*Merck Sharp & Dohme, Philadelphia, Pa.

DURATION OF THE DIET

The diet should be continued as long as there are significant gains in the mental level. The problem of evaluating mental growth brings up the importance of competent developmental testing. I.Q. or D.Q. tests should be obtained before treatment starts and at least once a year thereafter.

If the child has a significant gain in I.Q. the first year and then remains at the same level the following year, should the diet be discontinued? Some people have evidence to suggest that it might be, particularly if the child is over 4 years of age.[22, 23] However, whether and when it is safe to discontinue a low phenylalanine diet is as yet uncertain. This will be determined only by close observation of the progress of a number of these children who are taken off the diet. There are some who are hesitant to discontinue the diet of young children who are under good control[13, 15]; we share this view.

It is well known that phenylketonuria, in addition to causing mental retardation, has other untoward effects on the individual, such as irritability, epilepsy, and clouding of affect. A return of these features could cause a significantly adverse effect on the functioning of the child even if there were no decrease in I.Q. Certainly older children whose dietary treatment has been discontinued should have mental evaluations yearly.

Recent preliminary studies on older children with the disease and adults indicate that the secondary effects may be controlled by a modified low protein diet made up mostly of natural foods supplemented with a small amount of Lofenalac.

COST OF THE DIET

At the present time the special protein-substitute food costs from 75 cents to 2 dollars a day depending on the size of the child.

SUMMARY

The factors to be considered in the selection of children with phenylketonuria for dietary treatment are discussed. It is suggested that a trial on the diet be given to all children under 3 years of age and selected patients over 3 with I.Q.'s above 30.

The treatment of 10 infants and young children using the low phenylalanine formula, Lofenalac, has formed the basis of a simple plan of dietary management for phenylketonuria. The amounts of low phenylalanine formula and the amounts and kinds of other foods that should be given are presented in tabular form. Some sample menus are also given. Hospitalization is not necessary or desirable in order to initiate the diet. Frequent consultations with the family providing a chance for discussions and close moral support by the physician are likely to be of great importance.

The diet probably should be continued until the child is 3 years of age or older. We expect to continue the diet at least in modified form into the school years.

The basic constituents of the diet (calories, protein, and phenylalanine) plus phenylalanine serum levels are presented graphically. When the serum phenylalanine level was between 2 and 6 mg. per 100 ml., the phenylalanine intake averaged 18 mg. per pound of body weight per day.

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Phenylketonuria. II. Results of treatment of infants and young children

A report of 10 cases

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THIS is the second of a series of two articles on the dietary management[1] and results of treatment of phenylketonuria in infants and young children. This group of 10 children was on a special low phenylalamine diet over a period of from 6 months to 3 years. The basic diet food was Lofenalac.† In the preceding article[1] the details of dietary intake and the method of management were described. Each case can be followed by case number through the series.

This group represents all of the infants and children 3 years of age and under that were treated by us up to the time of preparation of this article. In no instance was the diet discontinued because of poor acceptance or because of failure to show an adequate mental response. Each of the 10 children is still on the diet. The group includes 4 babies started on the diet under 2 months of age, 1 at 8 months, and 5 children from 1 to 3 years of age.

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DATA

The results of treatment are presented in detail in the accompanying charts (*A-1* through *H-2*). Each letter represents a different family. The oldest child with phenylketonuria in a family is given No. 1, the next oldest child with phenylketonuria (if any) is given No. 2, etc. Each chart records the physical and mental development of one child while on the diet. Serum phenylalanine levels and representative electroencephalographic tracings are also given. Beneath the graph on each chart appears a brief description of the child, observations about changes which have taken place, and comments about

Table I. Most recent I.Q.'s* and D.Q.'s* of 10 treated children and their siblings

	Chronologic age (years-months)	*Mental or developmental age (years-months)*	*I.Q. or D.Q.*
Phenylketonuria (treated)			
A-1	6- 0	3- 7	60
A-2	2-10	2- 3	80
B-1	3- 0	3- 0	100
B-2	2- 0	2- 0	100
C-2	2- 9	2- 5	88
D-1	3- 6	2- 7	73
E-1	2- 1	1- 8	80
F-3	3- 6	2-10	80
G-2	2- 1	1- 1	52
H-2	0- 6½	0- 5½	82
Average			79.5
Phenylketonuria (untreated)			
Family C—brother	10- 0	0- 4	3
Family F—sister	12- 6	3-10	31
—sister	15- 0	1- 0	7
Family G—sister	6- 0	1- 8	28
Family H—brother	5- 6	2- 9	50
Average			23.8
Normal (nonphenylketonuria)			
Family A—brother	7- 8	7-10	102
Family D—brother	0- 6½	0- 7½	114
Family E—brother	6- 6	6- 6	100
—sister	8- 9	8- 6	97
—brother	11- 0	11-10	108
—brother	13- 1	15- 0	115
Family F—brother	5- 8	5- 4	94
—sister	11-11	11- 8	98
Family G—brother	8- 4	8- 7	104
Family H—sister	4- 6	4- 5	99
Average			103.1

*I.Q., intelligence quotient; D.Q., development quotient.

dietary control. Summaries of these data follow.

Intellectual development. The developmental status of each child was tested approximately every 6 months by the same clinical psychologist (V. A.) with the exception of one family which moved out of California (see footnotes, Charts *B-1* and *B-2*). Developmental age (D.A.) and developmental quotient (D.Q.) are referred to when the Gesell Developmental scale was used. The Gesell scale was used when the abilities of the person tested were less than those of an average 2-year-old. Mental age (M.A.) and intelligence quotient (I.Q.) are used when the basis for evaluation was the Revised Stanford Binet, which is appropriate only when mental development is at or above the 2 year level. Results of these tests are given on each child's chart and are presented together graphically in Fig. 1.

The babies placed on the diet before 2 months of age (A-2, B-1, B-2, H-2) are considered as a separate group. All were estimated to be within the normal range when the diet was started. All of the other 6 children, except the 2½-year-old boy (F-3), who had an initial estimated I.Q. of 80, were definitely retarded before the diet was started. The most recent I.Q.'s and D.Q.'s of all of the children are given in Table I. The average I.Q. is 79.5; the average of the 4 children treated before 2 months of age is 90.5. The average for the 6 children treated after 8 months of age is 72.2. Table I also gives the I.Q.'s and D.Q.'s of all of the siblings of the 10 treated children. The 5 siblings with untreated phenylketonuria have an average I.Q. of 23.8. The 10 normal siblings have an average I.Q. of 103.1.

Behavior patterns. The initial behavior of the children was often reminiscent of autism. Fear of unfamiliar things and avoidance of handling them were characteristic. Some also showed interest in spinning objects, walked in circles, and exhibited finger mannerisms. Other patterns sometimes asso-

Table II. Mental development of children with phenylketonuria in whom low phenylalanine diets were initiated sometime from the neonatal period to 3 years of age. A comparison is made with Knox's survey of the world's medical literature up to the beginning of 1960[3]

Mental development	*I.Q. or D.Q.*	*Knox's Survey (% of 43 cases)*	*Centerwall et al. (% of 10 cases)*
Severe retardation	0 to 19	7	0
Moderate retardation	20 to 49	39	0
Mild retardation	50 to 69	19	20
Borderline	70 to 79	2	10
Dull normal	80 to 89	7	50
Normal	90 to 110	26	20

ciated with neurological impairment such as hyperirritability, tiptoe gait, and gross tremor were also seen. However, despite some of the behavioral similarities to autism, none of the retarded children in this group showed indifference to social stimulation or avoidance of gaze.

On the diet, some of the earliest changes noted, often within a week, were increase in alertness, responsiveness, and attention span. The children became less irritable and slept better. These changes seemed to be correlated with the lowering of the serum phenylalanine levels. Conversely, one mother reported irritability in her child when the serum phenylalanine level later became elevated (above 10 mg. per 100 ml.), although she had no way of knowing that the level was higher than usual.

Motor abilities often improved rapidly, such as sitting, crawling, and walking. Speech and adaptive abilities usually developed less rapidly than motor functions; and fixations on more primitive behavior patterns, such as rocking and other repetitive movements, tended to persist. However in Patient A-1 in whom speech was totally lacking at 3 years of age before the dietary change, and was slow to appear, after 3 years of treatment, speech was on a par with improvement in other areas.

Physical growth. Heights, weights, and head circumferences during treatment were plotted on growth curves* which show the 16th, 50th, and 84th percentiles for age (median with plus and minus one standard deviation).

All of the children have been well nourished throughout the dietary period. Of the 6 children started on the diet after 8 months of age, 5 have maintained a growth pattern similar to that of the pre-diet period. One child (A-1) who initially was very stocky, lost weight precipitously when first placed on a diet. After being changed to Lofenalac, he ate well and maintained his weight in proportion to his height. Most of the significant drops in percentile levels occurred in the babies who were started on treatment before 2 months of age. The majority of the 10 children have developed as relatively short children, but well proportioned.

Serum phenylalanine levels. The initial serum phenylalanine levels before treatment are given on the individual charts and range from 9.8 (2½ days of age) to 63.5 mg. per 100 ml. Serum phenylalaline levels were taken on each child at intervals of 1 to 4 months while on the diet. The blood samples were usually drawn late in the afternoon, 3 to 5 hours after the last meal. The level was determined by a modified Kapeller-Adler reaction.[2]

When the children were first put on the diet, phenylalanine levels were determined at more frequent intervals until the levels were well controlled. The level was often down to normal in 1 week and usually by 2 weeks.

Our views as to the safe and optimum range within which to keep the serum phenylalanine levels have changed somewhat with the passage of time. In recent years we have attempted to keep the serum levels from 2 mg. to 6 ± 2 mg. per 100 ml.

Electroencephalographic findings. Electroencephalograms were taken before treatment (except in Case H-2) and representative samples of these and follow-up tracings are shown on each child's chart. All the electroencephalograms were done on an 8-channel, custom-designed machine in full-time clinical use. The children were awake and without sedation, and there was a minimum of 20 minutes on each tracing. Natural variations that occur at different ages were taken into consideration in the evaluations. All interpretations were made by one neurologist (L. M.).

Six of the 10 initial electroencephalograms were abnormal. Two of the 4 normal ones were on babies started on the diet under 2 weeks of age. After the diets were instituted, the electroencephalograms were

*Curves for weights and heights were adapted from the Iowa Growth Charts. Curves for head circumferences were adapted from data in Nelson's *Textbook of Pediatrics*, ed. 7, Philadelphia and London, 1959, W. B. Saunders Company, pp. 56-58.

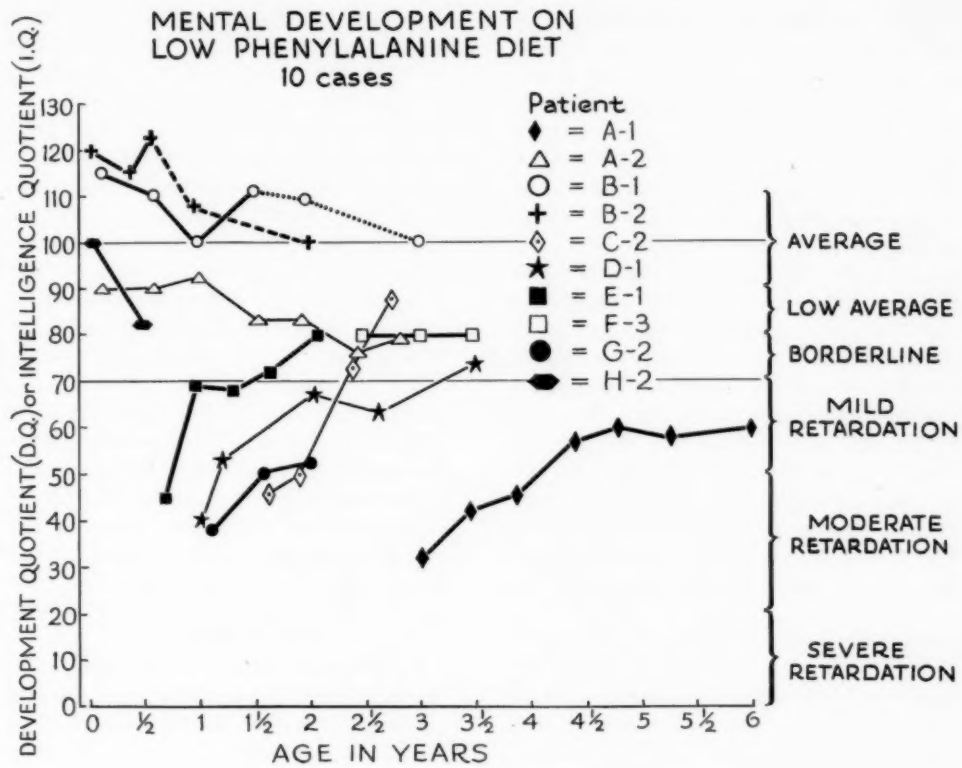

Fig. 1.

repeated approximately every 6 months. A total of 32 electroencephalograms were obtained.

During treatment, the electroencephalograms of all 6 of the children whose tracings had initially been abnormal became normal. This conversion took place after 1½ months to 2⅓ years (average 11½ months) on the diet. Two of the 4 children with initially normal tracings had developed mildly abnormal rhythms while on treatment, one of which has since returned to normal. None of the children had symptomatic epilepsy.

DISCUSSION

We are enthusiastic about the ease of management and the success of the treatment of phenylketonuria in infants and young children with the new low phenylalaline food, Lofenalac. The mothers had little or no difficulty in giving the diet, and the children were consistently well nourished. The serum phenylalanine levels were lowered to therapeutic levels within approximately two weeks, and subsequent control has been good. Early and significant improvement in behavior paralleled the decrease in the serum phenylalanine level. Continued improvement in behavior paralleled the improvement in intelligence. Mental retardation has been prevented thus far in the children started on the diet before 2 months of age. The original D.Q.'s of these 4 infants were necessarily estimates. The latest D.Q.'s on these children (some 6 months to 3 years later) average 90.5 and indicate a slight decrease of potential in spite of treatment. The 2 that seemed above average at first (Cases B-1 and B-2) now appear average; and the 2 that seemed average or slightly below (Cases

A-2 and H-2) now function in the dull-normal range. Comparing these children with normal siblings (Table I) reinforces the impression that there was some decrease in D.Q. However, in comparison to untreated siblings with phenylketonuria (Table I), there is little doubt that there has been great benefit from the diet.

The children whose development was retarded before treatment was started showed significant improvement. This group of 6 children placed on the diet at 8 months to 3 years of age had an average increase of 25 points in I.Q. One child, F-3, who had a relatively high I.Q. to begin with, showed no significant change during one year of treatment. We felt that a trial of treatment was justified because his prognosis on a normal diet was not known. If this child is excluded, the 5 children who were retarded initially had an average gain of 30 I.Q. points per child.

Additional insight into effects of diet management is gained by comparing the treated children with their untreated siblings (or with other untreated individuals as was done by Knox[3]). These data indicate that without dietary treatment children with phenylketonuria become relatively more retarded as they grow older. This is our opinion after observing the arrested development of these children at early stages. The actual benefit of the diet to the baby with phenylketonuria is greater, therefore, than the measure of his I.Q. gain while on treatment since it also apparently includes the prevention of a further decrease.

In Table II the mental development of our 10 children is compared with that of the 43 children treated under 3 years of age recently compiled from the world medical literature by Knox.[3] The data are treated essentially as in Knox's article except that the I.Q. groupings have been changed to be more in accord with the conventional classification. The greater percentage of our children with I.Q.'s of 80 or above is at least partially accounted for by the larger percentage of small infants in our series.

The most obvious difference between the two groups is that the Knox series has a large percentage of children with I.Q.'s under 50. This seems to indicate that these children received little benefit from the diet. In our group the children with initially low I.Q.'s made significant gains, and there are none at present with I.Q.'s under 50. Although a series of 10 cases is too small for statistically significant conclusions, it might be expected that as the diet has been improved and management made easier, there would be larger proportions of patients responding well to treatment.

The progress of one child (E-1) was followed simultaneously by another clinic.* Several developmental tests were made independently by them and afforded a unique opportunity for later comparison. The results were well correlated. Tests at the other clinic* during the 16 months of dietary treatment showed a steady increase in D.Q. from 37 to 87. During this same period our tests showed a steady rise from 45 to 80.

It must be concluded that although mental retardation can be prevented by initiation of a low phenylalanine diet in early infancy, the diet may not afford complete protection. Also, young children whose development is retarded before treatment show a variability of response but probably are never restored to their normal potentials. This must be kept in mind when one is counseling parents. A longer follow-up of all these children and others reported in the medical literature will be necessary to evaluate adequately the final results of dietary treatment.

Observations on physical growth show that the children's heights tend to be below average, but their weights have been in good proportion to their heights. In that untreated children with phenylketonuria also tend to be smaller than average, it appears that the low phenylalanine diet may have little effect on the usual pattern of physical growth.

All of the children were on daily supplementary vitamins and iron. Hemoglobin determinations were made every few months

*Child Development Clinic of Childrens Hospital, Los Angeles.

and serum protein electrophoresis once or twice a year. There was no anemia, and total serum proteins remained in the normal range. On scattered occasions there appeared to be a slight relative depression of the gamma and beta fractions of the globulins; but these changes were not specific to the time of diet management, and there were no apparent associated symptoms. Similar observations have been made by other investigators.[4, 5]

It is reasonable to speculate that there may be some unrecognized deficiency in the special diet. We were concerned by the limitation of natural food supplements when the serum phenylalanine was kept down to normal levels (about 1 to 3 mg. per 100 ml.). It seemed that the lack of natural food elements or perhaps the low phenylalanine itself might be causing the limited physical growth. For this reason more food supplements and somewhat higher serum levels (2 to 8 mg. per 100 ml.) subsequently were allowed. During both periods, physical growth and mental development continued at about the same rate. It will be necessary to analyze the course of many infants with well-documented serum levels in order to come to a conclusion about safe and optimal serum phenylalanine levels. Until then, a suggested range, which seems within the limits of safety, is from 2 to 6 mg. per 100 ml. of serum and perhaps 2 to 4 mg. per 100 ml. during the first year of life.

The head circumference data were evaluated (Charts *A-1* through *H-2*) in order to determine if there was any positive correlation of head size with prognosis. Some of the cases, i.e., G-2 and F-3, would support this view but, for the group, the variation is too great for drawing conclusions.

The electroencephalographic findings are in accord with previous studies of patients with the disease on low phenylalanine diets.[6] Eight of the 10 children have had abnormal tracings at some time during the observation period, including 2 who changed from normal to slightly abnormal rhythms while on the diet. Most of the tracings showed mild to moderate generalized dysrhythmias without characteristic patterns or localization. At the latest evaluations all but one had normal electroencephalograms. Most frequently the electroencephalograms showed early improvement which paralleled or exceeded clinical improvement. The conversion from abnormal to normal took place after 1½ months to 2⅓ years (average 11½ months) on the diet.

SUMMARY

The results of dietary treatment of 10 infants and young children with phenylketonuria with a low phenylalanine diet (Lofenalac) from 6 months to 3 years (average 22½ months per child) are presented. The group includes 4 babies started on the diet under 2 months of age, 1 at 8 months, and 4 from 1 to 3 years.

The data include weights, heights, head circumferences, serum phenylalanine levels, electroencephalographic findings, personality and intelligence changes, and brief notes on individual diet control patterns. The following observations were made:

1. Initial changes in behavior paralleled the decrease in the serum level of phenylalanine, which usually was within the "therapeutic range" one to two weeks after starting the diet. The children became less irritable and less withdrawn, and their responsiveness and attention span were increased.

2. The 4 children who were placed on the diet prior to 2 months of age are developing within the normal and low-normal range.

3. The 6 children started on the diet from 8 months to 3 years of age have an average I.Q. of 72.

4. Ten normal siblings have an average I.Q. of 103, and 5 untreated siblings with phenylketonuria have an average I.Q. of 24.

5. The children generally had somewhat slow growth patterns but were well nourished for their heights. Little difficulty was experienced in giving the special diet. There were no complications of the treatment such as diarrhea, marked weight loss, or anemia. One young infant (H-2) had an unexplained severe rash for several months dur-

ing early treatment.

6. Serum phenylalanine levels were usually maintained within a range of 1 and 8 mg. per 100 ml.

7. Six of the 10 children initially had abnormal electroencephalograms; 2 of the 4 normal electroencephalograms were on infants started on the diet while under 2 weeks of age. Of the latest tracings during the dietary treatment, only one of the 10 was abnormal. Conversion from abnormal to normal took place after 1½ months to 2⅓ years (average 11½ months) on the diet.

Ada W. Turner, B.A., Editor of Official Publications, College of Medical Evangelists, gave valuable assistance in preparation of the manuscripts of this and the companion article on phenylketonuria.[1] Lucille C. Innes, medical artist, Audiovisual Service, College of Medical Evangelists, prepared the charts and graphs. Edward N. Hamilton, Director, Audiovisual Service, College of Medical Evangelists, and Dorene Yuen, photographer, followed the children of these reports with serial photographs and movies, selections from which illustrate these articles.

We acknowledge with appreciation the referral of patients in these reports from Joseph A. Garrisi, M.D. (B-1); Harold E. West, M.D. (A-1); Lon B. Klink, M.D., and Warren Harris, M.D. (H-2); Charles A. Neff, M.D. (G-2); Richard Koch, M.D. (E-1); and the North Hollywood Well-Child Conference of the Los Angeles City Health Department (D-1).

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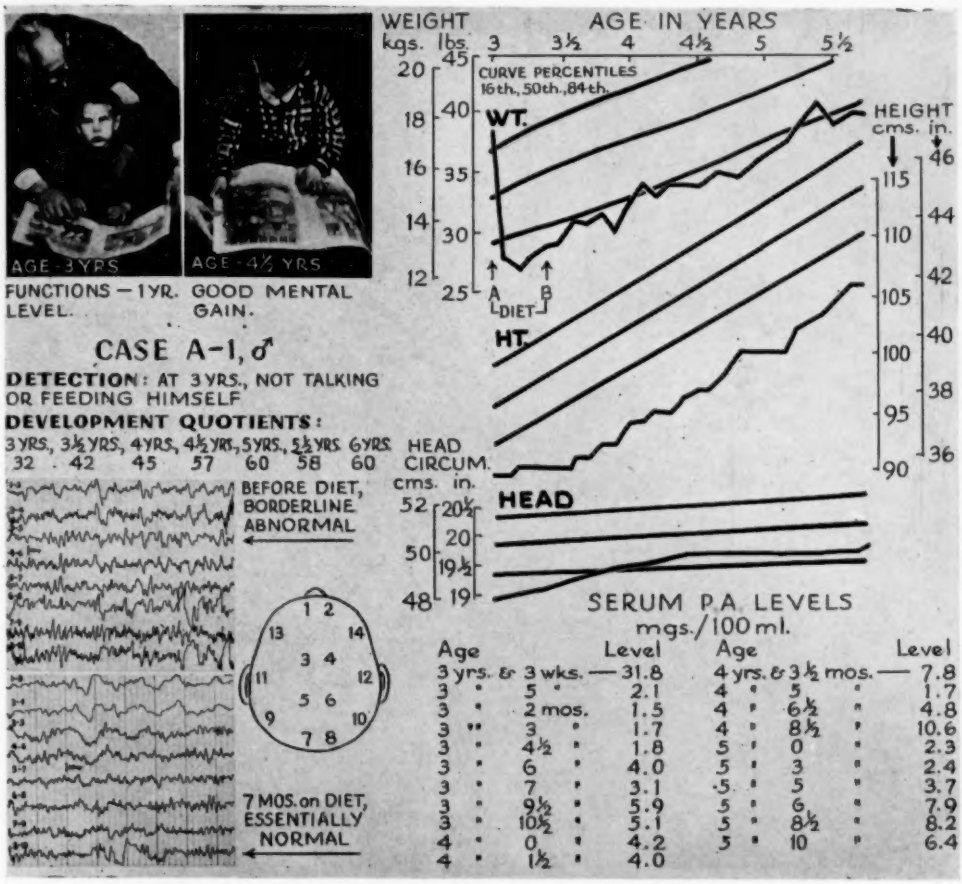

AGE 3 YRS
AGE 4½ YRS
FUNCTIONS — 1 YR. LEVEL.
GOOD MENTAL GAIN.
CASE A-1, ♂
DETECTION: AT 3 YRS., NOT TALKING OR FEEDING HIMSELF
DEVELOPMENT QUOTIENTS:
3 YRS., 3½ YRS., 4 YRS., 4½ YRS., 5 YRS., 5½ YRS. 6 YRS.
32 42 45 57 60 58 60
BEFORE DIET, BORDERLINE ABNORMAL
7 MOS. on DIET, ESSENTIALLY NORMAL
WEIGHT
kgs. lbs.
AGE IN YEARS
3 3½ 4 4½ 5 5½
CURVE PERCENTILES 16th., 50th., 84th.
WT.
HT.
HEIGHT
cms. in.
A DIET B
HEAD CIRCUM.
cms. in.
HEAD
SERUM P.A. LEVELS
mgs./100 ml.
Age Level
3 yrs. & 3 wks. — 31.8
3 " 5 " 2.1
3 " 2 mos. 1.5
3 " 3 " 1.7
3 " 4½ " 1.8
3 " 6 " 4.0
3 " 7 " 3.1
3 " 9½ " 5.9
3 " 10½ " 5.1
4 " 0 " 4.2
4 " 1½ " 4.0
Age Level
4 yrs. & 3½ mos. — 7.8
4 " 5 " 1.7
4 " 6½ " 4.8
4 " 8½ " 10.6
5 " 0 " 2.3
5 " 3 " 2.4
5 " 5 " 3.7
5 " 6 " 7.9
5 " 8½ " 8.2
5 " 10 " 6.4

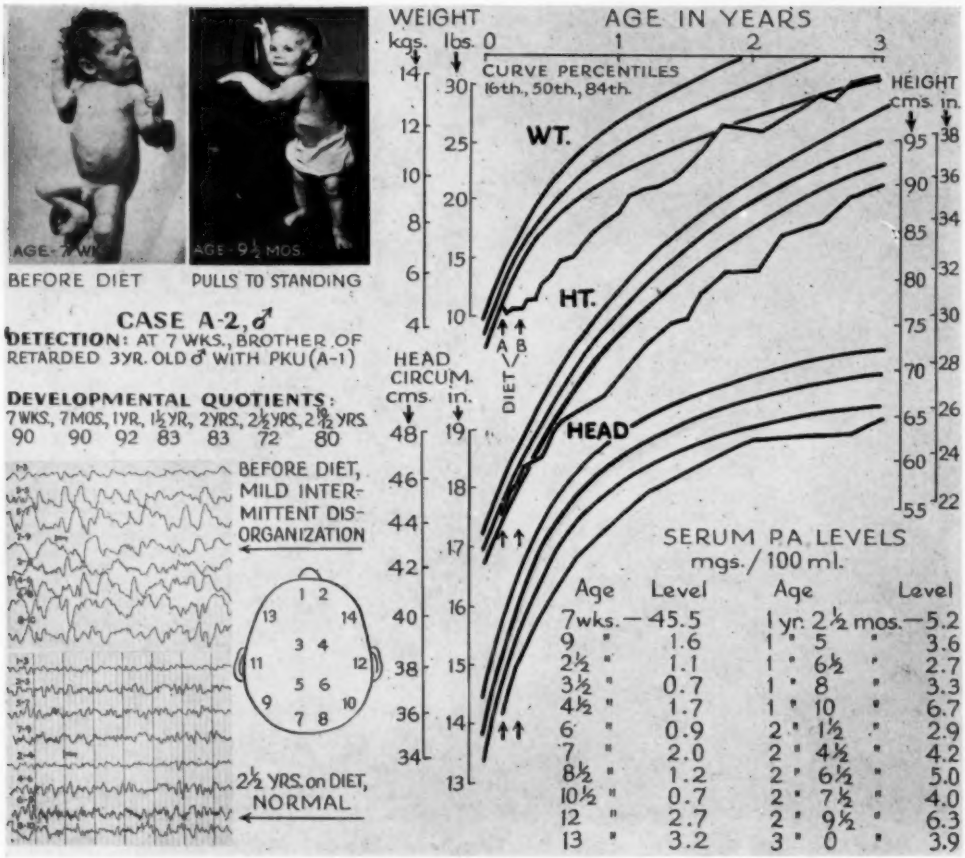
Case A-1. The 2 younger of the 3 children in this family have phenylketonuria. The mother is of Irish-Bohemian descent and the father of German-Swedish descent. On psychological examination at 3 years of age, this boy was judged to have a Gesell D.Q. of 32. Fine manual coordination was at the 10- to 12-month level but some aspects of gross motor development were comparable to the 1½-year level. Speech was absent and there was no evidence that he comprehended any words other than his name. His behavior was very difficult, and violent protests were accompanied by diffuse trembling. Objects presented to him were struck at or thrown away.

At 3½ years of age after 6 months on the diet, there was a conspicuous change in this boy, more apparent in his calm, cooperative, adaptable behavior than in intellectual performance, although the D.Q. had increased to 42. There was still no speech, but comprehension of simple verbal directions was clear. A retest at 4 years of age showed continued behavioral improvement and mental growth. At 5 years of age speech had emerged approximating 2½-year patterns and he was able to attain an I.Q. of 60 on the Binet.

He now attends a nursery school for retarded children. He is a friendly and cooperative child, responsive to praise and approval.

This boy was just past his third birthday when he was placed on a low phenylalanine diet. In appearance he was alert, husky, and well developed. The parents begged to have him on the diet when his baby brother was put on and we consented. The first diet given was a casein hydrolysate powder mixed with oil and sugar. He did not take this diet willingly, lost weight precipitously, and after 4½ months was changed to Lofenalac as indicated on the chart. After this he began to gain satisfactorily. He has been taking the Lofenalac as a double strength beverage (1 measure to an ounce of water). For some time he ate mostly canned peaches from the list of supplementary natural foods, but now he eats a wide variety of these foods.

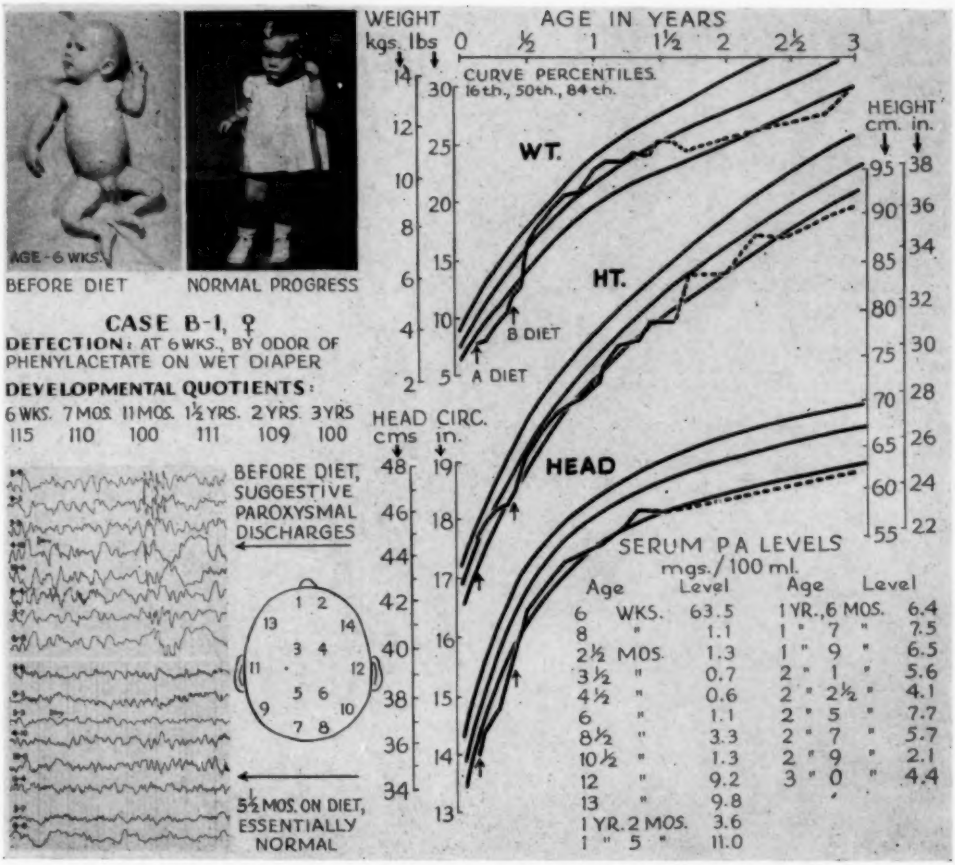
In the graph above Diet *A* refers to Ketonil and Diet *B* to Lofenalac.


AGE - 7 WKS.
AGE - 9½ MOS.
BEFORE DIET
PULLS TO STANDING
CASE A-2, ♂
DETECTION: AT 7 WKS., BROTHER OF RETARDED 3YR. OLD ♂ WITH PKU (A-1)
DEVELOPMENTAL QUOTIENTS:
7 WKS. 7 MOS. 1 YR. 1½ YR. 2 YRS. 2½ YRS. 2½ YRS.
90 90 92 83 83 72 80
BEFORE DIET, MILD INTERMITTENT DISORGANIZATION
2½ YRS. on DIET, NORMAL
WEIGHT
kgs. lbs.
AGE IN YEARS
CURVE PERCENTILES 16th., 50th., 84th.
WT.
HT.
HEAD
HEIGHT
cms. in.
HEAD CIRCUM.
cms. in.
DIET
A B
SERUM PA LEVELS
mgs./100 ml.
Age Level Age Level
7 wks. — 45.5 1 yr. 2½ mos. — 5.2
9 " 1.6 1 " 5 " 3.6
2½ " 1.1 1 " 6½ " 2.7
3½ " 0.7 1 " 8 " 3.3
4½ " 1.7 1 " 10 " 6.7
6 " 0.9 2 " 1½ " 2.9
7 " 2.0 2 " 4½ " 4.2
8½ " 1.2 2 " 6½ " 5.0
10½ " 0.7 2 " 7½ " 4.0
12 " 2.7 2 " 9½ " 6.3
13 " 3.2 3 " 0 " 3.9

Case A-2. The 2 younger of the 3 children in this family have phenylketonuria. The mother is of Irish-Bohemian descent and the father of German-Swedish descent. When this child was first seen for evaluation at 7½ weeks, development was adjudged to be average, but qualitatively response seemed of somewhat inferior caliber. He was a wiry baby, tense, restless, and fretful, and attention seemed inferior. When seen at 32 weeks, he had recently been ill and appeared thin, small, tense, and hyperactive. Liberal scoring on the Gesell Developmental Scale resulted in a D.Q. of 90. By 18 months of age, when his health was good, the D.Q. was rated as 83, and later examinations gave even slightly lower ratings. He continued to be hyperactive, with a short attention span. Personal-social behavior was immature but essentially normal. He sat alone at 9 months, walked holding on at 11 months, and walked alone at 15 months.

This child was a consistently poor eater of solid foods and has taken relatively small quantities of concentrated formula (21 tbsp. of Lofenalac in 16 ounces of water at 2 years of age). He took only about 5 ounces of supplementary foods, and several ounces of milk were added daily. In retrospect, it seems that this child was functioning at a D.Q. of about 80 from the time he was first seen. He has probably been maintained at about the same level; however, the values are given here as they were originally recorded.

In the graph above Diet *A* refers to Ketonil and Diet *B* to Lofenalac.


AGE - 6 WKS.
BEFORE DIET
NORMAL PROGRESS
CASE B-1, ♀
DETECTION: AT 6 WKS., BY ODOR OF PHENYLACETATE ON WET DIAPER
DEVELOPMENTAL QUOTIENTS:
6 WKS. 7 MOS. 11 MOS. 1½ YRS. 2 YRS. 3 YRS
115 110 100 111 109 100
BEFORE DIET, SUGGESTIVE PAROXYSMAL DISCHARGES
5½ MOS. ON DIET, ESSENTIALLY NORMAL
WEIGHT kgs. lbs
AGE IN YEARS 0 ½ 1 1½ 2 2½ 3
CURVE PERCENTILES 16th., 50th., 84th.
WT.
HT.
HEAD
B DIET
A DIET
HEIGHT cm. in.
HEAD CIRC. cms in.
SERUM PA LEVELS mgs./100 ml.
Age Level Age Level
6 WKS. 63.5 1 YR., 6 MOS. 6.4
8 " 1.1 1 " 7 " 7.5
2½ MOS. 1.3 1 " 9 " 6.5
3½ " 0.7 2 " 1 " 5.6
4½ " 0.6 2 " 2½ " 4.1
6 " 1.1 2 " 5 " 7.7
8½ " 3.3 2 " 7 " 5.7
10½ " 1.3 2 " 9 " 2.1
12 " 9.2 3 " 0 " 4.4
13 " 9.8
1 YR. 2 MOS. 3.6
1 " 5 " 11.0

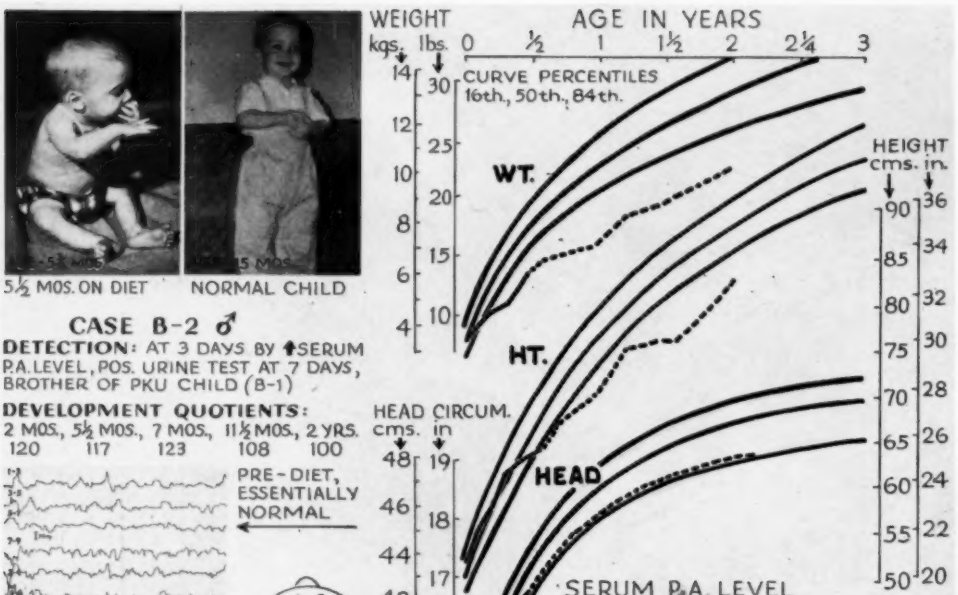
Case B-1. The 2 older of the 3 children in this family have the disease. The mother is of English-Scotch-Swedish descent and the father of Irish descent. At 7½ weeks of age this infant girl appeared stable and mature in behavioral patterns for her age level. She slept and ate well, was attentive and socially responsive, and was reported to smile and laugh aloud. Muscle tone seemed normal, but she was observed to be easily startled—not violently, but one startle was followed by several others and then by gross trembling.

She was rechecked periodically, at 32 weeks, at 1 year, and at 1½ years. The easy startling and gross tremor were never observed after the first examination. The consistent picture was of a sturdy, stable, well-developed child, rather quiet and stolid, but vigorous and enthusiastic in her response when interested. She maintained a better than average level of development in all areas. Since the family moved from California this child has been followed by other doctors* who have supplied data on her growth and development, dietary intake, and serum phenylalanine levels. This part of the growth curve is represented on the graphs by broken lines.

This baby seemed to have no trouble learning to like the Lofenalac drink, and by the time she was 1 year of age she was taking almost a quart of double strength (40 calories per ounce) formula. With this she took approximately one 4¾-ounce can of fruit and one of vegetables, about 2 tbsp. of rice cereal, and 3 animal cookies daily. This satisfied her completely.

In the graph above Diet *A* refers to Ketonil and Diet *B* to Lofenalac.

*We wish to express our appreciation to the following physicians: Charles W. Streamer and Frederick A. Horner of Denver, Colorado, and Donald Fraser and M. W. Partington of Toronto, Canada.


5½ MOS. ON DIET
NORMAL CHILD
CASE B-2 ♂
DETECTION: AT 3 DAYS BY ↑SERUM P.A. LEVEL, POS. URINE TEST AT 7 DAYS, BROTHER OF PKU CHILD (B-1)
DEVELOPMENT QUOTIENTS:
2 MOS., 5½ MOS., 7 MOS., 11½ MOS., 2 YRS.
120 117 123 108 100
PRE-DIET, ESSENTIALLY NORMAL
6 MOS. on DIET, ESSENTIALLY NORMAL
WEIGHT kgs. lbs.
AGE IN YEARS 0 ½ 1 1½ 2 2¼ 3
CURVE PERCENTILES 16th., 50th., 84th.
WT.
HT.
HEAD
HEIGHT cms. in.
HEAD CIRCUM. cms. in
SERUM P.A. LEVEL mgs./100 ml.
Age Level Age Level
BIRTH 4.0 7 mos. 2.4
3 days 15.0 8 " " 4.3
7 " 30.0 11½ " 2.6
11 " 40.0 13 " 5.7
(DIET STARTED) 14½ " 4.2
24 days 0.6 17 " 0.4
34 " 1.9 18½ " 0.1
2½ mos. 2.0 21 " 9.4
5 " 1.7 2 YRS. 3.8

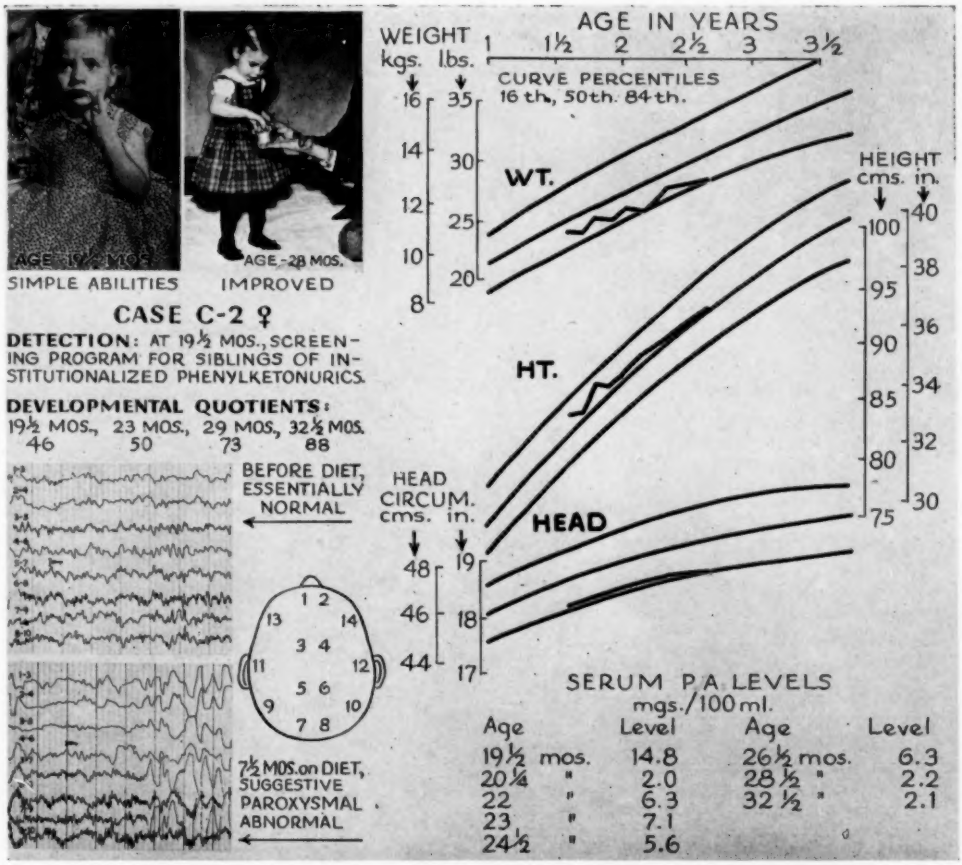
Case B-2. The 2 older of the 3 children in this family have phenylketonuria. The mother is of English-Scotch-Swedish descent and the father of Irish descent. This child was seen at our center for psychological evaluation at 8 weeks of age (6½ weeks after starting the diet*), at 24 weeks, and finally at 30 weeks (when the family moved out of the state). At the first examination he appeared well developed, relaxed, attentive and responsive, and above average in maturation. At 24 and 30 weeks of age his progress was evaluated as definitely above average. He appeared healthy and vigorous, with good motor development, normal social responsiveness, and discrimination; and his attention, interest, and adaptive behavior were especially good for his age. Developmental quotient was found to be high average.

He accepted the Lofenalac formula readily and had no digestive problems. After he was 3 months of age, small amounts of selected baby foods were added much the same as with a normal baby. He sat alone just before he was 6 months, pulled to standing at 6½ months, and walked at 13½ months.

Since the family moved from California, this child has been followed by other doctors,† who have supplied data on his growth and development, dietary intake, and serum phenylalanine levels. This part of the growth curve is represented on the graphs by broken lines.

*Diagnosis by elevated serum phenylalanine level at 3 days of age was accomplished through the cooperation of Nino Ferrero, M.D., and the nursery personnel of the Good Samaritan Hospital, Los Angeles.

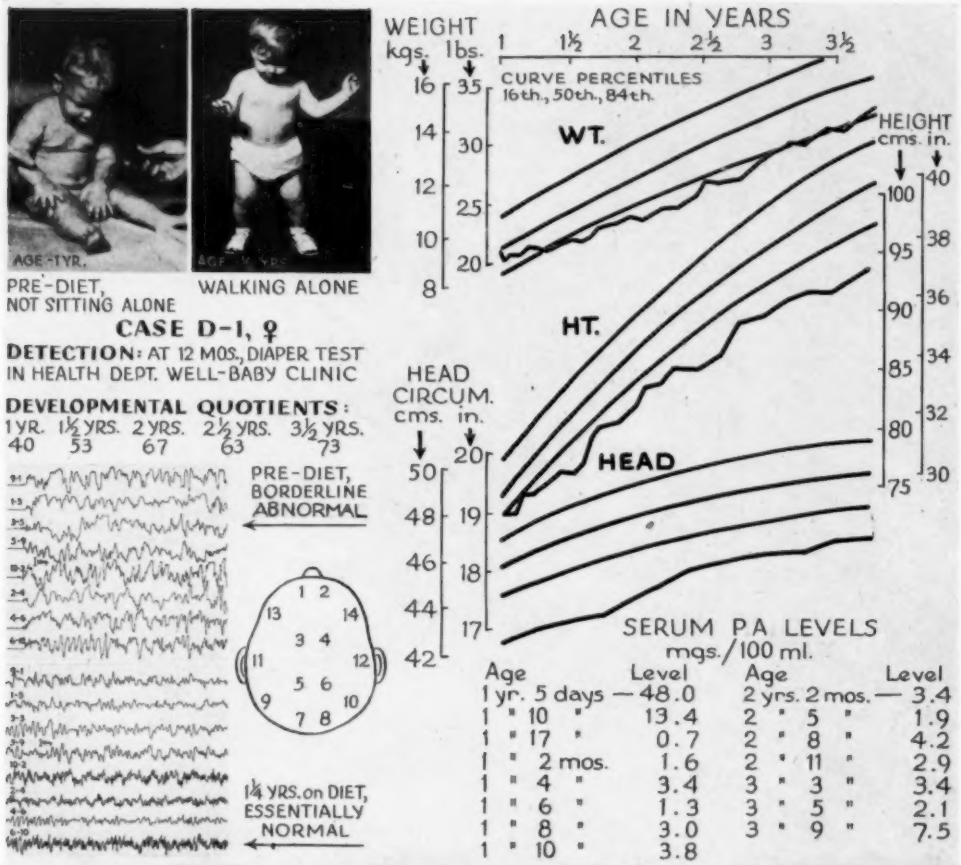
†We wish to express our appreciation to the following physicians: Charles W. Streamer and Frederick A. Horner of Denver, Colorado, and Donald Fraser and M. W. Partington of Toronto, Canada.


AGE 19½ MOS.
AGE 28 MOS.
SIMPLE ABILITIES
IMPROVED
CASE C-2 ♀
DETECTION: AT 19½ MOS., SCREENING PROGRAM FOR SIBLINGS OF INSTITUTIONALIZED PHENYLKETONURICS.
DEVELOPMENTAL QUOTIENTS:
19½ MOS., 23 MOS., 29 MOS., 32½ MOS.
46 50 73 88
BEFORE DIET, ESSENTIALLY NORMAL
7½ MOS. on DIET, SUGGESTIVE PAROXYSMAL ABNORMAL
WEIGHT kgs. lbs.
AGE IN YEARS
1 1½ 2 2½ 3 3½
CURVE PERCENTILES 16th, 50th, 84th.
WT.
HT.
HEAD
HEIGHT cms. in.
HEAD CIRCUM. cms. in.
SERUM P.A. LEVELS mgs./100 ml.
Age Level Age Level
19½ mos. 14.8 26½ mos. 6.3
20¼ " 2.0 28½ " 2.2
22 " 6.3 32½ " 2.1
23 " 7.1
24½ " 5.6

Case C-2. There are 2 children in this family and both of them have phenylketonuria. The mother comes from northern European stock and the father is of Norwegian descent. This patient was given her first psychological examination at 1 year, 8 months of age; she was then an attractive baby just learning to walk. Since the mother had difficulty getting her to drink the Lofenalac beverage, it was suggested that she mix the powder with the supplementary food. The child has been taking a daily diet of about 1 cup of fruit and ½ to 1 cup of vegetables with 20 measures of Lofenalac plus 2 cookies. This simple diet works so well that the mother rarely uses special recipes.

On initial examination the child's motor development far exceeded other abilities. She had no speech and a short attention span. She withdrew from strangers, and was fretful. She walked repetitively in a circle, self-absorbed. After 3 months on the low phenylalanine diet, this behavior had largely disappeared, but little acceleration of mental growth was noted. She still scratched at surfaces and objects and was obsessively occupied with listening to the sounds elicited by hitting different objects. On these first two examinations, Gesell D.Q.'s were estimated at 46 and 50.

There was a marked change when she was seen after 9 months on the diet. Social response was much more friendly. There was no stereotyped behavior or preoccupation with sounds. Speech was still meager, but performance had advanced rapidly and in the form board test approached expectations for her age. Retesting 3 months later at 2 years, 9 months showed further advances to an I.Q. of 88 on the Revised Stanford Binet. She was friendly, responsive, and composed, and showed an active interest in the testing. Her speech was still limited, but response to simple commands was at the 3-year level. Some poor coordination and poor finger dexterity were still present.

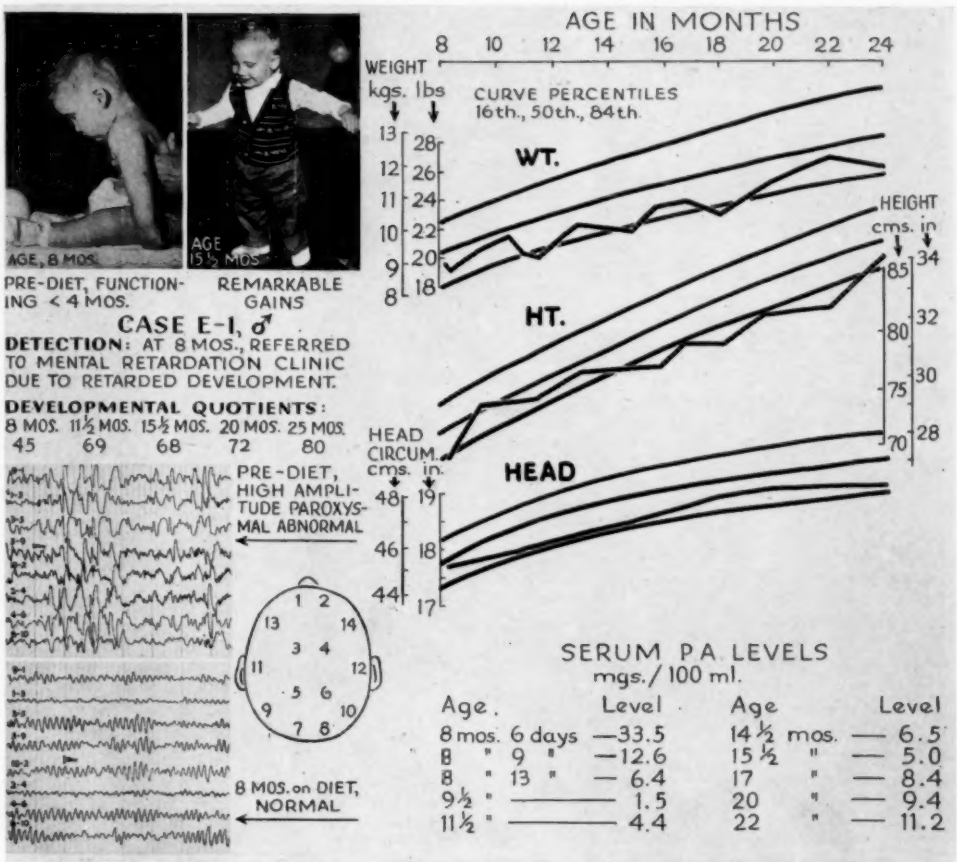

AGE 1 YR.
PRE-DIET, NOT SITTING ALONE
WALKING ALONE
CASE D-1, ♀
DETECTION: AT 12 MOS., DIAPER TEST IN HEALTH DEPT. WELL-BABY CLINIC
DEVELOPMENTAL QUOTIENTS:
1 YR. 1½ YRS. 2 YRS. 2½ YRS. 3½ YRS.
40 53 67 63 73
PRE-DIET, BORDERLINE ABNORMAL
1¾ YRS. on DIET, ESSENTIALLY NORMAL
WEIGHT kgs. lbs.
AGE IN YEARS
1 1½ 2 2½ 3 3½
CURVE PERCENTILES 16th., 50th., 84th.
WT.
HT.
HEAD
HEIGHT cms. in.
HEAD CIRCUM. cms. in.
SERUM PA LEVELS mgs./100 ml.
Age Level
1 yr. 5 days — 48.0
1 " 10 " 13.4
1 " 17 " 0.7
1 " 2 mos. 1.6
1 " 4 " 3.4
1 " 6 " 1.3
1 " 8 " 3.0
1 " 10 " 3.8
Age Level
2 yrs. 2 mos. — 3.4
2 " 5 " 1.9
2 " 8 " 4.2
2 " 11 " 2.9
3 " 3 " 3.4
3 " 5 " 2.1
3 " 9 " 7.5

Case D-1. This family has 2 children, the older of whom has phenylketonuria. The mother is of Irish-Swedish-French-American Indian descent and the father of Irish-Swedish-German descent. When first seen at the age of 1 year this little girl was unable to sit alone and seemed immature for her chronological age. She was, however, a responsive baby.

Originally she seemed to show steady but retarded development, with a D.Q. of 40 on the Gesell Developmental Scale. After 2½ months on the phenylalanine-restricted diet, definite advance in rate of mental growth was indicated by a D.Q. of 60. She soon learned to sit and was walking alone by 18 months of age.

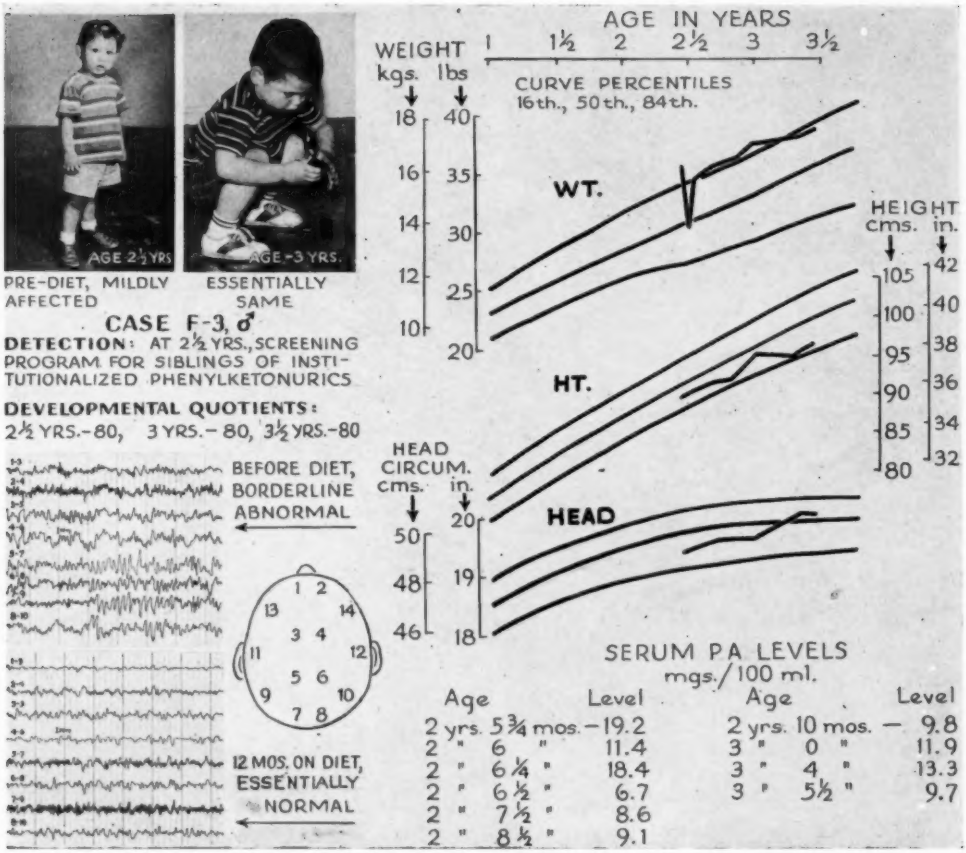
As has been noted in most of the children with phenylketonuria who were not treated until after the first year of life, powers of attention have appeared weak and unstable and speech development has been relatively slow. On examination at 2 years of age, she was observed to walk repetitively in circles, at times to stiffen and shake rigidly, run rapidly and stiffly on her toes, and squeal. By the age of 3½ years the behavior described was no longer observed. She jabbered incessantly, with some recognizable words and short sentences, but speech was unintelligible except to the initiated. She adjusted in the youngest age group of a nursery class and was enthusiastic about school. Her I.Q. was 73 on the Binet.

Initially, this little girl's daily diet consisted of 25 measures of Lofenalac in 1 quart of water. She took this well and was satisfied by it so that intake of supplemental low protein foods was self-limited to approximately 2 ounces per day. It was necessary, therefore, to add about 3 ounces of milk to her formula to prevent phenylalanine deficiency. Over the course of several years of dietary management, growth has been satisfactory, but abnormal eating habits have persisted.


AGE, 8 MOS.
AGE 15½ MOS.
PRE-DIET, FUNCTIONING < 4 MOS.
REMARKABLE GAINS
CASE E-1, ♂
DETECTION: AT 8 MOS., REFERRED TO MENTAL RETARDATION CLINIC DUE TO RETARDED DEVELOPMENT.
DEVELOPMENTAL QUOTIENTS:
8 MOS. 11½ MOS. 15½ MOS. 20 MOS. 25 MOS.
45 69 68 72 80
PRE-DIET, HIGH AMPLITUDE PAROXYSMAL ABNORMAL
8 MOS. on DIET, NORMAL
AGE IN MONTHS
8 10 12 14 16 18 20 22 24
WEIGHT
kgs. lbs
CURVE PERCENTILES
16th., 50th., 84th.
WT.
HEIGHT
cms. in
HT.
HEAD CIRCUM.
cms. in.
HEAD
SERUM PA LEVELS
mgs./100 ml.
Age Level Age Level
8 mos. 6 days —33.5 14½ mos. — 6.5
8 " 9 " —12.6 15½ " — 5.0
8 " 13 " — 6.4 17 " — 8.4
9½ " ——— 1.5 20 " — 9.4
11½ " ——— 4.4 22 " — 11.2

Case E-1. This child, the last of 5 children, is the only one in the family with phenylketonuria. The mother is of English-German descent and the father of Irish-Dutch descent. At 8 months of age this heavy, pallid baby boy was amiable, contented, and underactive. His musculature was hypotonic, and he appeared to have little voluntary control over movement. Although he showed attention and response to objects and would retain and wave objects placed in his hands, he never reached for anything. By Gesell standards his D.Q. was estimated as 45, but hints of higher potential were recognized. He sat alone at 10 months; and when he was tested again at 12 months his physical appearance had changed markedly. He was no longer limp and helpless but able to control and direct body movement. There was marked improvement in all areas of performance, and his D.Q. was estimated at 69. He walked alone at 15½ months. He seemed friendly, pleasant, and was "into everything." Motor development was slightly retarded but qualitatively normal, and speech was beginning. He continued to show improvement in subsequent tests.

This child has taken his Lofenalac drink well; about 1 quart of 1½ strength formula daily is supplemented with a variety of low-protein foods. As the youngest of a number of children, and having also a good appetite, he has been difficult to control in respect to diet. The progress has been dramatic, and psychological evaluations by another clinic have closely correlated with the D.Q.'s reported here.

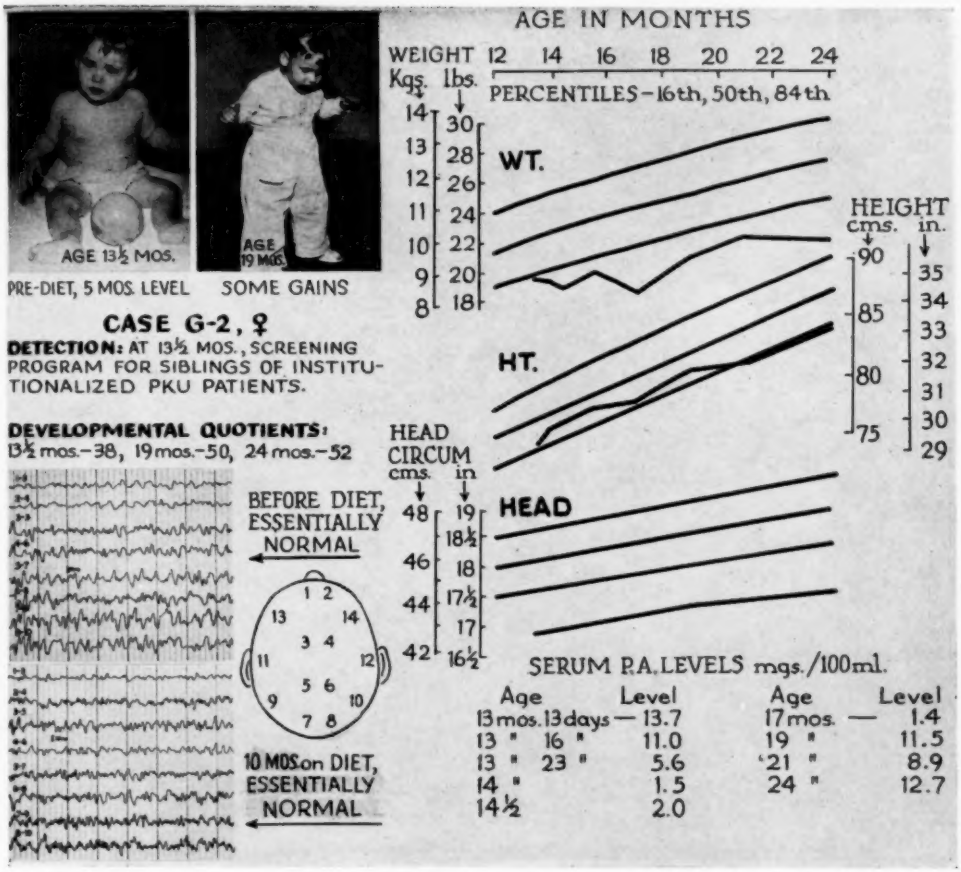

AGE 2½ YRS.
AGE-3 YRS.
PRE-DIET, MILDLY AFFECTED
ESSENTIALLY SAME
CASE F-3, ♂
DETECTION: AT 2½ YRS., SCREENING PROGRAM FOR SIBLINGS OF INSTITUTIONALIZED PHENYLKETONURICS
DEVELOPMENTAL QUOTIENTS:
2½ YRS.-80, 3 YRS.-80, 3½ YRS.-80
BEFORE DIET, BORDERLINE ABNORMAL
12 MOS. ON DIET, ESSENTIALLY NORMAL
AGE IN YEARS
1 1½ 2 2½ 3 3½
WEIGHT kgs. lbs
CURVE PERCENTILES 16th., 50th., 84th.
WT.
HT.
HEAD
HEIGHT cms. in.
HEAD CIRCUM. cms. in.
SERUM PA LEVELS mgs./100 ml.
Age Level
2 yrs. 5¾ mos. – 19.2
2 " 6 " 11.4
2 " 6¼ " 18.4
2 " 6½ " 6.7
2 " 7½ " 8.6
2 " 8½ " 9.1
Age Level
2 yrs. 10 mos. – 9.8
3 " 0 " 11.9
3 " 4 " 13.3
3 " 5½ " 9.7

Case F-3. The first 2 and the last of the 5 children in this family have the disease. Both parents are of Mexican descent. Attempts to examine this child psychologically have been unsatisfactory because of his extreme resistance to unfamiliar people and surroundings. He clung to his mother and screamed persistently if she left him. The mother stated that he was always "like this" with strangers. However, his play interests and interactions with siblings and neighborhood children have seemed fairly normal.

He was a sturdy, healthy-looking boy, who seemed adequate in motor skills and understood and carried out simple directions. The only performance elicited during the first testing sessions (under direct pressure of threats and bribes from his mother) met 2-year standards satisfactorily.

After 6 months on the diet he was re-examined. He was then 3 years of age, and there had been no striking change in his behavior or in the level of his performance. His mother said he was beginning to speak a little more but still used few words. It was estimated that he was functioning at the borderline level or better. Subsequent tests also have been unsatisfactory and have revealed no essential change in I.Q.

This little boy is the youngest in a permissive Mexican family with 3 older siblings at home. In spite of good intentions, it has obviously been a problem for the mother to restrict the diet as prescribed. He takes the Lofenalac as a beverage made 1½ times normal strength, evidently without difficulty, but he has access to extra food. This has resulted in slightly higher serum phenylanaline levels than were hoped for.

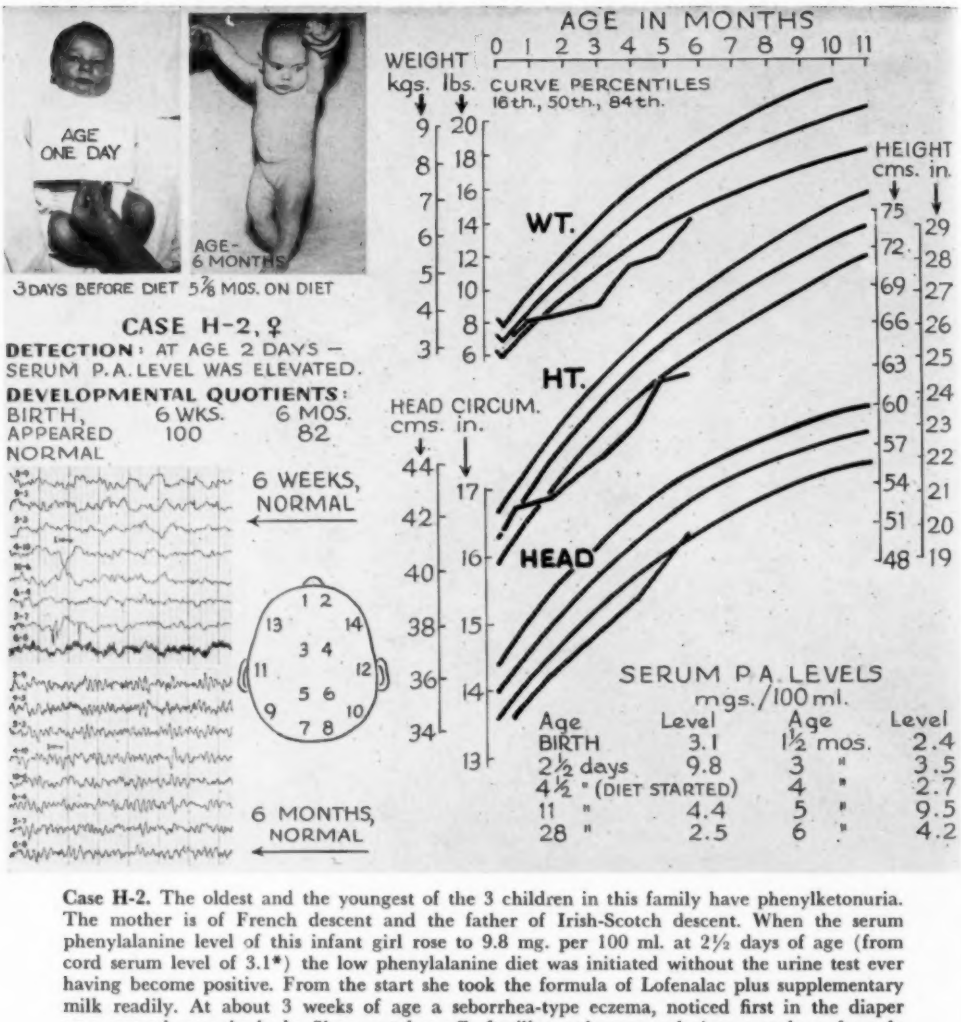


Case G-2. The 2 younger of the 3 children in this family have phenylketonuria. The mother is of Jewish and the father of Italian descent. When first seen for psychological evaluation, at 13 months of age, this pretty little girl was unable to bring herself to a sitting position. Her D.Q. was estimated as 38 by Gesell standards. She enjoyed being held, and there was no apparent discrimination among people. She vocalized spontaneously, using a repetitive "ta-ta" in response to social stimulation. There was considerable finger posturing, and from time to time she would become rigid and shake all over (this behavior was not believed to be true convulsions).

When offered an object, she would draw her arm back away from it or scratch and hit at it. Later she grasped, with a crude palmar grasp, a red block which she excitedly vocalized over and mouthed.

After 6 months on the phenylalanine-restricted diet, at 19 months of age, she was beginning to walk alone, and the parents reported marked improvement in mood. She was more ready to manipulate and exploit materials, but banging objects and then releasing them with a slight cast remained the predominant activity. Attention appeared weak and unstable and speech was limited to a few single words. Her D.Q. rating at this time was around 50, a significant gain. However, at 2 years of age her D.Q. was still only 52.

She drinks her Lofenalac formula in a slightly concentrated strength. She is not a good eater and sometimes has taken almost no other food. It has been necessary to add milk to her formula to keep the phenylalanine level up to normal. She walked at 19 months, 5½ months after starting the diet.


AGE ONE DAY
AGE-6 MONTHS
3 DAYS BEFORE DIET
5⅞ MOS. ON DIET
CASE H-2, ♀
DETECTION: AT AGE 2 DAYS — SERUM P.A. LEVEL WAS ELEVATED.
DEVELOPMENTAL QUOTIENTS:
BIRTH, APPEARED NORMAL
6 WKS. 100
6 MOS. 82
6 WEEKS, NORMAL
6 MONTHS, NORMAL
AGE IN MONTHS
0 1 2 3 4 5 6 7 8 9 10 11
WEIGHT kgs. lbs.
CURVE PERCENTILES 16th., 50th., 84th.
WT.
HT.
HEAD
HEIGHT cms. in.
HEAD CIRCUM. cms. in.
SERUM P.A. LEVELS mgs./100 ml.
Age Level Age Level
BIRTH 3.1 1½ mos. 2.4
2½ days 9.8 3 " 3.5
4½ " (DIET STARTED) 4 " 2.7
11 " 4.4 5 " 9.5
28 " 2.5 6 " 4.2

Case H-2. The oldest and the youngest of the 3 children in this family have phenylketonuria. The mother is of French descent and the father of Irish-Scotch descent. When the serum phenylalanine level of this infant girl rose to 9.8 mg. per 100 ml. at 2½ days of age (from cord serum level of 3.1*) the low phenylalanine diet was initiated without the urine test ever having become positive. From the start she took the formula of Lofenalac plus supplementary milk readily. At about 3 weeks of age a seborrhea-type eczema, noticed first in the diaper area, spread over the body. She was taken off of milk supplement and given a soybean formula supplement and local treatment. Thereafter there was slow but progressive clearing of the skin until the rash was completely cleared by 5 months of age. Her diet has been increased to include fruits and vegetables.

To verify the diagnosis of phenylketonuria, at 4 months of age she was placed on a full protein soy milk formula. After 2 days the urine test became faintly positive for the first time, and the serum phenylalanine level had climbed from 2.7 to 22.6 mg. per 100 ml. She was immediately placed back on the low phenylalanine formula.

At the time of her first psychological test at 6 weeks, this baby appeared normal for her age. She had severe eczema and was fussy; but she quieted at the sound of a bell. Her expression was alert, and she responded to social stimulation. At 6 months her responses were those of a normal healthy baby, but she did not support herself as well or explore as actively as average for her age. She appeared to be functioning at approximately the 5 month level (D.Q. 82). One hesitates to attach prognostic significance to a one month delay in developmental abilities at 6 months of age.

*Through the cooperation of James L. Slater, M.D., and the nursery personnel of the Methodist Hospital of Southern California, Arcadia, Calif.

TROPICAL PEDIATRICS

Magnesium balance studies in marasmic kwashiorkor

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KINGSTON, JAMAICA

PROTEIN malnutrition in infants is often associated with gross electrolyte disturbance. Analysis of muscle biopsy specimens and of urinary collections has shown that the magnesium content of muscle is reduced as well as the potassium, and that the output of magnesium in the urine may remain low for many weeks during recovery.[1] Taken together, these facts suggest a depletion of body magnesium. However, the low urinary magnesium might be due not to efficient renal conservation but to inefficient intestinal absorption in the malnourished state.

Balance studies have therefore been made on 3 malnourished infants, whose case histories are briefly summarized below. Balances were carried out intermittently over periods of 40 to 50 days during recovery. Magnesium intake was varied by oral supplementation initially and after apparent repletion. Muscle biopsies were also performed on admission and after clinical recovery.

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MATERIAL

The subjects were Jamaican infants presenting the picture of marasmus and gastroenteritis together with minor features of the kwashiorkor syndrome.

Case 1. A male, aged 9 months, weighing 4.6 kilograms, presented with a history of diarrhea and vomiting for 6 weeks. He had previously been fed on inadequate amounts of breast milk and skim milk. On admission he was febrile, dehydrated, and wasted without edema. There was scaling dermatosis in the flexures and purpuralike spots were present on the limbs. There were no hair changes, and the liver was not enlarged. Investigations disclosed the following: hemoglobin 11.2 Gm. per cent; serum sodium 130, potassium 3.6, magnesium 1.87, chloride 90, and carbon dioxide 32 mEq. per liter; serum albumin 2.0, globulin 2.9 Gm. per cent; liver fat 22 per cent of wet weight (11 per cent on recovery). The stools showed no pathogens.

Fig. 1.

Fig. 2.

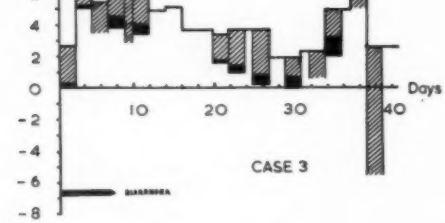

Fig. 3.

Figs. 1-3. Daily magnesium balance data in 3 cases of marasmic kwashiorkor during recovery. The abscissa represents the number of days from admission. Magnesium intake is plotted on the ordinate above the base line.
Solid black indicates urinary excretion in milligrams; diagnonal lines, fecal excretion in milligrams. An open base to the column signifies that there was no urine collection.

The child took graded feeds well with potassium, magnesium, and phosphate supplements, and had no diarrhea initially. However, in spite of rapid clinical improvement, weight gain was very slow (1.6 kilograms in 12 weeks) and there was a late relapse of diarrhea.

Case 2. A male, aged 13 months, whose weight after loss of edema was 3.5 kilograms, had a history of intermittent diarrhea and vomiting for 4 months. His diet had consisted of glucose water and sweetened condensed milk only. On admission he was gravely ill, with wasting, fever, dehydration, acidosis, and anemia. There was mild edema, but no dermatosis or hepatomegaly. Investigations showed the following: hemoglobin 5.2 Gm. per cent; serum sodium 140, potassium 3.6, magnesium 1.73, chloride 97, and carbon dioxide 13 mEq. per liter; serum albumin 1.6, globulin 3.0 Gm. per 100 ml. The stools showed no pathogens.

Intravenous electrolyte therapy was given for 48 hours. Diarrhea and clinical dehydration persisted for a week in spite of a course of chloramphenicol; the edema was lost in 4 days. Serum electrolytes on the eighth day were: sodium 136, potassium 4.6, chloride 100, and carbon dioxide 15 mEq. per liter. The anemia responded fully to folic acid. Although diarrhea recurred twice in the first 3 weeks, the child's condition caused no anxiety after the first week and there was a weight gain of 3 kilograms in 2 months.

Case 3. A male, aged 20 months, whose weight after loss of edema was 4.4 kilograms, had a history of intermittent diarrhea, vomiting, and edema for a year, with cough and anorexia for a month. He had been fed on skim milk and condensed milk, but no solid food.

On admission he was extremely wasted, with anemia, mild edema, hair changes, skin ulcers, and respiratory infection. There was no hepatomegaly. The results of investigations were as follows: hemoglobin 6.8 Gm. per cent; serum sodium 128, potassium 3.6, chloride 98, magnesium 1.35, and carbon dioxide 20 mEq. per liter; serum albumin 2.3, globulin 2.8 Gm. per cent; liver fat 17 per cent of wet weight. There were no pathogens in the stools.

Graded oral feeds were tolerated with potassium, magnesium, and phosphate sup-

plements. The edema was lost in 4 days. Severe diarrhea persisted for 5 days, and on the eighth day the serum electrolytes were: sodium 120, potassium 5.0, and chloride 100 mEq. per liter. The anemia responded fully to folic acid. Weight gain was slow for 5 weeks, but thereafter very rapid. This child became markedly constipated on a milk and leaf-protein mixture during the "recovery" balance period.

METHODS

Total fecal collections were made in 2 day lots for periods of up to 16 days; and urine collections were made for as many as possible of these 48 hour periods. Stool markers were not considered necessary because of the frequency of stools. The practical limitations of balance studies in these malnourished infants have been discussed previously.[2]

Muscle biopsies were obtained under local anesthetic from the pectoral muscle in the anterior axillary fold. The first biopsy was performed within a week of admission, and the second biopsy from 57 to 89 days after admission.

Magnesium was estimated in the various biologic fluids by flame spectrophotometry as described elsewhere.[3]

RESULTS

The magnesium balance figures are represented in Figs. 1 to 3. In all cases a positive balance was established after admission. In Case 1, about half of the ingested magnesium was absorbed initially; high oral supplementation did not greatly increase the total absorption. In Case 3, on the other hand, the supplement was largely absorbed even in the presence of diarrhea, and it can be assumed that there was a positive balance of at least 30 mEq. in 9 days.

Although the figures for urinary magnesium output are incomplete, the output has been shown to be so consistently low initially that it can reasonably be concluded that this slight discrepancy does not affect the over-all picture. Low renal excretion persisted in 2 cases until equilibrium occurred in the balances. There was greater renal excretion in Case 3, however, in which there was the highest magnesium absorption.

Table I. Electrolyte content of muscle (values in milliequivalents per kilogram wet weight)

	First biopsy			*Second biopsy*		
Case	*Mg*	*K*	*Na*	*Mg*	*K*	*Na*
1	7.8	53	73	9.2	64	60
2	7.1	29	77	11.3	72	76
3	9.0	50	62	13.5	72	70
Mean	8.0	44	71	11.3	69	69
Normal infants (Dickerson and Widdowson[17])		20.0			89.5	50

After 7 weeks, when there appeared to be equilibrium, an added magnesium supplement was almost entirely rejected by Cases 2 and 3 (fecal excretion in Case 3 was delayed by constipation) whereas it led to a further positive balance in Case 1, but with high urinary excretion.

Muscle analyses confirmed a severe deficiency of magnesium and potassium and an increased sodium content initially, with some reversion toward normal 8 to 12 weeks later (Table I). The magnesium deficit in recovery was greatest in Case 1, which may correlate with the retention of the second supplement in this case.

DISCUSSION

The intracellular space. The muscle electrolyte changes recorded here are very substantial, and are similar to those observed in an earlier series.[1] At first sight the figures based on wet weight (Table I) suggest a severe relative decrease in intracellular fluid in the initial specimen. Such a decrease is clearly apparent in histologic cross-sections of the muscle. It is significant however that the concentrations of intracellular cations are low even when related to noncollagen nitrogen. Waterlow and Mendes[4] found a mean increase of 16 per cent in potassium content per milligram noncollagen nitrogen during recovery, which compares with a 30 per cent increase per milligram wet weight in a total of 15 cases described above and

previously.[1] The increase in magnesium content in the same series was 38 per cent. Further unpublished data of Waterlow and Smith agreed with those of Frenk and his associates[5] in showing no significant change in potassium content in relation to dry weight. On a wet weight basis the water content of the initial specimen was on an average 2 per cent higher than after recovery. Although this difference is small it means that the total solid content of the tissue per unit wet weight is reduced by one-tenth. For example, in the normal child, water may be 78 per cent, solids 22 per cent; in the malnourished, water may be 80 per cent, solids 20 per cent.

A tentative interpretation of these data is that at least half of the initial magnesium and potassium deficit is due to a decrease in intracellular volume, coincident with the loss of intracellular solids, particularly protein. The remainder of the magnesium and potassium deficit indicates a true loss of intracellular electrolytes in relation to protein. It is not apparent from the present data whether the latter is associated with a normal intracellular water content or whether, as is held by the Mexican school,[6] there is intracellular "overhydration" together with partial replacement of potassium by sodium.

Growth requirements. The balance studies indicate that magnesium is retained in large quantities during recovery. In Case 3 it appears that the positive balance amounted to about 40 mEq. in the first 3 weeks. In this period the gain in body weight was only 0.5 kilograms, but studies of total body water[7] and indirect measurements of muscle mass[8] suggest that the gain in body tissue during this stage is relatively much greater, being masked by a loss of excess body water.

A considerable proportion of positive magnesium balance may therefore be attributed to expansion of the cellular mass in the process of recovery. Some is due to correction of a true intracellular deficit in the soft tissues. The persistence of a high sodium content in the second biopsy specimen suggests that correction of the intracellular deficit tends to precede the cellular expansion.

In addition to soft-tissue repletion, it seems from the quantities involved that much of the retained magnesium enters the bony skeleton. Analyses of total body magnesium[9] suggest that a normal infant's 5 kilograms of weight contains approximately 150 mEq. of magnesium, and it has been estimated that half the body's magnesium is in bone.[10] Although there is only slow skeletal growth during the early weeks of recovery from protein malnutrition there may well be a build up of depleted magnesium "stores" in bone. Little is known about the nature of these stores or their lability in deficiency states. Eliel and associates[11] have concluded that magnesium is situated in the hydration shell of bone crystals, and should be readily available for ionic exchanges. In severely magnesium-deficient rats, MacIntyre and Davidsson[12] observed a decline in magnesium concentration in the femur to half that of controls. MacIntyre,[13] however, believes that extracellular bone magnesium is not a freely available reservoir.

Urinary excretion of magnesium. It is apparent from these studies that very low urinary magnesium levels indicate a deprivation of the ion. Increased urinary excretion, however, is not necessarily a sign of repletion, as it may depend to some extent on the amount absorbed from the diet. High supplementation with efficient absorption in Case 3 gave rise to moderate urinary excretion, whereas in Case 2 when the supplement was poorly absorbed the urinary excretion remained low.

In the previous series[1] a low urinary output of magnesium persisted for long periods. Supplements had not been given. The late rise in excretion coincided not only with repletion of tissue magnesium but in some cases with a high magnesium intake on the commencement of a mixed diet.

The present observations confirm earlier findings in human experimental subjects that there is a sensitive renal regulatory mechanism which responds to a reduced magnesium intake even though the serum magnesium

levels are unaltered.[14, 15] It has also been shown that various experimental procedures affecting renal magnesium excretion do not correlate either with renal plasma flow or plasma magnesium concentration.[16] It therefore seems justifiable to speak of a true renal conservation of magnesium in both experimental and natural deficiency states.

SUMMARY

Studies of magnesium balance were made on 3 Jamaican infants during recovery from marasmic kwashiorkor.

Analyses of muscle biopsy specimens indicated a marked deficit of magnesium as well as of potassium in all cases. The serum magnesium level was slightly low in one case. A positive magnesium balance was maintained for several weeks in recovery and was accompanied by low urinary excretion. In one case there was considerable intestinal absorption of magnesium, even in the presence of diarrhea. Efficient absorption of a high oral supplement tended to overcome renal conservation.

Previous analysis has suggested that the deficiency of intracellular electrolytes in wet muscle samples is due partly to the reduced intracellular volume associated with protein loss and partly to a true electrolyte deficit. The positive magnesium balance in recovery is therefore attributable both to intracellular repletion and to tissue growth; the latter tends to be masked clinically by loss of excess body water. Little is known of the additional factor of the repletion of magnesium in bone, but the evidence from animal experiments is that the deficit in bone may be very substantial.

I am grateful to Professor J. C. Waterlow, Director of this Unit, for helpful criticism.

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Subcutaneous phycomycosis in an East African child

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SUBCUTANEOUS phycomycosis has been reported recently in Indonesian children by Lie Kian Joe and colleagues[1-4] as an entity with suggestive clinical features and with diagnostic histologic and mycologic findings.

The present paper presents an account of a case in an East African child from northern Uganda and suggests that, as in Indonesia,[1] the condition may not be rare.

CASE REPORT

Ogweng, a 6-year-old Lango boy from near Lira in northern Uganda, was admitted in April, 1960, with a history of swelling of the arm, anterior and posterior chest, and neck on the left side which had started in the middle of the upper arm over a year previously and had subsequently progressed. There was no known antecedent history of insect bite, thorn puncture, or other trauma. There was no pain or fever, and the child appeared to be active, lively, and in good health, save for the weight of the affected arm which had to be supported by the other hand (Fig. 1).

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Examination. There was no abnormality except for the swelling, which was confined to the left side of the body and involved the inframandibular region, the anterior and posterior chest walls, and the circumference of the upper arm and the upper third of the forearm. The lower two thirds of the forearm and the hand were unaffected and normal in appearance. The swelling was quite painless, nontender, and did not itch. It was composed of a sheet of hard-as-wood subcutaneous induration with a definite, easily palpable peripheral edge, with, in some places, outlying hard nodules of about 1 to 5 cm. in diameter. The whole thickening was intimately connected with the overlying skin, but was freely mobile on the deeper tissues. There was no pitting edema or evidence of acute inflammation. The overlying skin was not ulcerated; there was no enlargement of regional lymph nodes.

Investigations. The blood count showed hemoglobin, 11 Gm. per cent; white blood cells, 6,600 per cubic millimeter; polymorphonuclear leukocytes, 33 per cent; lymphocytes, 51 per cent; and eosinophils 12 per cent. Blood film for malaria and blood films for microfilaria (day and night) were negative. Skin snips (for onchocerciasis) were negative. Urine (for cells, casts,

and chemical determinations) was normal; stools, ascaris ova positive. Chest and arm x-ray was normal, except for soft tissue swelling. The tuberculin test (Heaf) and Kahn test were negative.

Biopsy. This was carried out in three regions and all showed extensive foreign body granulomatous reaction characterized by small foci of round cell infiltration, foreign body giant cells, and numerous eosinophils, with associated fibrous tissue reaction. Further study of the sections (by P. C. B.) showed the presence of the large, branching hyphae with surrounding cuffing with eosinophilic material (Fig. 2).

DISCUSSION

Malignant lymphoma[5, 6] (which is common in Uganda) was excluded by the biopsy, although the history of chronicity of the disease also made this diagnosis untenable. Filarial elephantiasis was made unlikely by the absence of involvement of the forearm and hand and by the nodular structure of the edge of the swelling, while there was no marked eosinophilia and no circulating microfilaria, by day or night.

The clinical appearance was striking; in retrospect, almost exactly identical with the description by Lie Kian Joe and his colleagues[1-4] of affected Indonesian children. As they state, the typical condition appears to consist of "localized, painless, subcutaneous swelling, covered with intact skin, occupying a large area of the body, and lasting for months."[1] The diagnosis is suggested histologically by the eosinophilic granulomatous reaction and confirmed by finding large, branching hyphae in the tissue sections.[1, 4]

Lie Kian Joe and his associates note that the mode of infection is unknown. In some of their cases there has been a tendency to spontaneous regression.

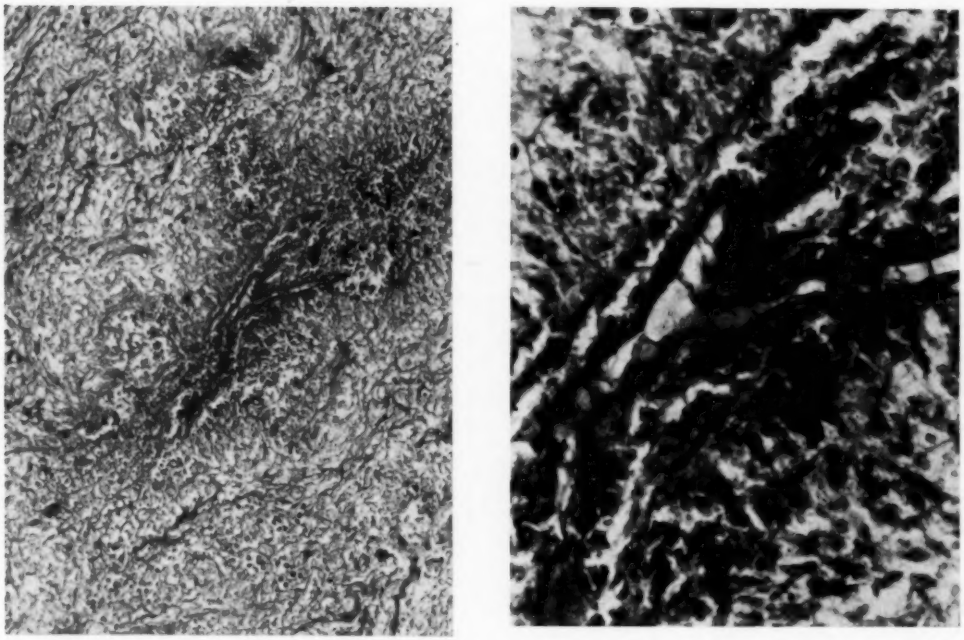
In the United States, Canada, and the United Kingdom, phycomycosis has been described as occurring elsewhere in the body, including the lungs, brain, ears, and gastric wall, often in otherwise severely ill subjects (e.g., with leukemia, cirrhosis, etc.) in which fungicemia appeared to have taken place terminally.[1] In Durban, South Africa, 7 of 22 cases with visceral involvement were in children with kwashiorkor.[7]

Subcutaneous lesions seem to be unusual in the temperate zone, although a case, apparently responding to orally administered potassium iodide, has been reported from Canada.[8]

It has been suggested that different fungi of the class Phycomycetes can cause "this distinctive and characteristic lesion," and from 4 of Lie Kian Joe's cases a Basidiobolus species was identified at culture.[4] Mycologic culture was not possible in the present case, although, on examination of the sections, Dr. C. W. Emmons of the National Institutes of Health, Bethesda, agreed that "the fungus conspicuously present in the

A *B*

Fig. 1. Subcutaneous phycomycosis in East African child. *A*, Anterior view. *B*, Posterior view. (The ulceration near the medial aspect of the elbow is due to the biopsy wound.)



A **Fig. 2.** Histologic appearance. *A,* Low power, showing central hyphae with surrounding eosinophilic cuffing. *B,* High power, showing detailed structure of hyphae. *B*

tissues closely resembles *Basidiobolus ranarum*."

Subcutaneous phycomycosis seems, according to present evidence, principally to affect children. Five infections have been reported in Indonesian children,[1-4] and one has been seen in a Dutch girl who had been resident in Indonesia.[9] However, in Indonesia, according to Lie Kian Joe and co-workers, it is possibly "not very rare." The same probably applies in Uganda, as other clinically suggestive cases have been seen in recent years, of which most, but not all, have been in children. Detailed clinical and pathologic findings will be discussed elsewhere.[10, 11]

A tendency to spontaneous regression has also been noted in some cases, but this could not be ascertained in the present child as he could not be traced. Whether treatment is either indicated or effective is not known, but the possibility of using either potassium iodide orally or one of the newer fungicides, such as amphotericin B, plainly merits consideration.

SUMMARY

A case of subcutaneous phycomycosis in a 6-year-old African boy from northern Uganda is presented. The main characteristic features were: (1) a slowly spreading, painless, subcutaneous induration, (2) no other obvious clinical signs or positive routine laboratory tests (and, in particular, no *marked* eosinophilia), and (3) histologic appearance, at biopsy, of eosinophilic granulomatous tissue and the presence of the branched hyphae of phycomycosis.

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MEDICAL PROGRESS

Living with epileptic seizures

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THE primary purpose in the therapy of any disability is the rehabilitation of the patient to a life as nearly normal as possible within the limitations of his disability. In epilepsy the efforts to control the seizures are, of course, of primary importance. But whether full control is achieved or whether recurrent seizures persist, there remain many problems concerning the psychological management of the patient and his parents and their relationship to the social milieu in which they live.

The medical treatment for epilepsy today is effective in the control of seizures in about 60 per cent of cases. The number of seizures in another 25 per cent can be cut down until they are hardly a handicap. In the remaining 15 per cent, the seizures are refractory to all of the available forms of therapy. The methods of treatment of epilepsy employed in our clinic have been previously described.[1-3]

In many instances, patients who have severe, intractable epilepsy (the 15 per cent group) are forced to live a life of invalidism or at least semi-invalidism. For some of these patients institutional care may be the only recourse.

This paper deals with some of the problems which the epileptic patient encounters (both the patient whose seizures are controlled and the one who has infrequent seizures) and contains recommendations concerning the assistance which the physician can offer.

The epileptic patients with controlled seizures frequently have to cope with the unwarranted stigma which many of the laity attach to the disorder of epilepsy. In addition, many of those patients who have infrequent seizures are also disturbed psychologically by fears and anxieties which stem from the anticipation of subsequent seizures.

The conditions which surround each case are so varied that only general advice can be offered here. Principles and methods which we have found to be effective will be discussed, but it should be realized that no set of rules can be applied indiscriminately to each case. The data presented and discussed in this paper were compiled from information obtained (from physicians and patients) over the course of a prolonged follow-up study made on thousands of epileptic patients. Many of these patients were observed for 20 to 25 years.

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ROLE OF THE PHYSICIAN

Attitude of physician. It appears that some physicians still have the impression that epilepsy is the most serious of the convulsive disorders and also that it is a hopeless and intractable condition. This attitude was reflected by a general practitioner who was seen as a patient in our clinic. At the start of the interview this physician said: "I certainly hope I do not have epilepsy." We were unable to establish a cause for his convulsions. We, therefore, told him that our diagnosis was a convulsive disorder of undetermined etiology (or epilepsy). We explained to him that his disorder, in all probability, would be much more serious if we had been able to discover a cause. After thinking the matter over for a moment or so, he agreed. As he left the consultation room, he said: "Gee, I certainly am glad I only have epilepsy." This attitude is extreme, but illustrative.

Some physicians have adopted the policy of concealing the word epilepsy from the parents of epileptic children. Clinics have been established throughout the country dealing with convulsive patients and terms such as "convulsive clinics" or "seizure clinics" have been assigned instead of the term "epilepsy clinic." In several instances when we asked why these terms were employed instead of the term "epilepsy clinic," we received the following answer: "I do not wish to 'stigmatize' our clinic with the term epilepsy."

We do not believe that one can "hide" the word epilepsy from the older children or their parents. The term is used in medical textbooks, is seen by the public in newspapers and magazines, and is heard on radio and television broadcasts. We believe that it is best to face this problem honestly. We explain first that the term epilepsy is derived from the Greek word "epilepsia" which, when translated into English, means "seizure." We also tell them that the term epilepsy is assigned to those patients who suffer with convulsions or seizures for which a definite cause cannot be established.

Importance of explaining the handicap to the patient. There is no doubt that most epileptic patients with infrequent seizures can be rehabilitated to the extent that they can live an essentially normal life. The patient must realize that he has a handicap and that he must adjust his life accordingly. He should be told that this can usually be accomplished by learning to "live with his seizures."

He should be encouraged to disregard the layman's adverse attitude toward epilepsy. He should realize that he, himself, cannot correct the ignorance and prejudices of the general public which undoubtedly stem from misunderstanding of the disorder. This latter advice is exceedingly important. Many of our patients became pathologically resentful, belligerent, and antagonistic after having made many fruitless attempts to convince certain individuals that they were not "different people" or "second-rate citizens."

The patient should be emphatically told that there is no reason why epilepsy should carry a stigma; and, second, that it is a disorder differing in no way in its social implications from rheumatic fever, tuberculosis, or diabetes. He should also be told that the misunderstandings concerning epilepsy undoubtedly will gradually disappear as the public becomes more and more aware of the real nature of the disorder.

Frequency of visits. The physician should see the epileptic patient at frequent intervals in order to discuss his social problems. It is true that many competent general practitioners are exceedingly busy and may not have sufficient time to see the individual patient often enough to discuss adequately these problems. In such instances, they should refer the patient to one of the lay epilepsy associations (if available in their community). The names of some of these organizations are listed in Putnam's book[4]; others are currently being established in various communities throughout the country. We have found that many patients are helped considerably by taking an active part in these organizations.

A recent survey made at our clinic indicated that approximately one out of 50

people will develop some type of epilepsy during their lifetime.[5, 6] Certainly there is not a sufficient number of psychiatrists and physicians specializing in epilepsy to care for the vast number of epileptic patients.

Keeping records. Generally, we advise our patients and/or their parents against keeping written records of the frequency of spells. Many of them told us that they were instructed by their physician that it was absolutely necessary to keep a detailed written report of spells in order that he could adequately evaluate the efficacy of their medication. We believe that such procedures may cause patients and/or their parents much more harm emotionally than it can benefit the physician medically. We have found, in many instances, that it keeps them constantly aware of the illness. We stress the policy of "trying to forget about the seizures" and advise the patients and/or their parents merely to keep a mental note of frequency of spells. As far as the physician is concerned, we believe it is important that he know approximately how many spells the patient has had during intervals between visits, but not necessarily the exact number. In those, for example, who suffer with petit mal epilepsy the physician could get only an approximate idea of the frequency of spells since many such spells go unobserved.

The physician should study the patient's seizure pattern very carefully in order to determine whether he has a well-defined aura. An aura, particularly one of long duration, is a very important aspect of the seizure pattern. With this knowledge, the patient frequently can protect himself from injury or from exposure of seizure to the public, if he is in a precarious or exposed situation at the time of onset.

We also believe that the parent or associate should be warned against constantly asking the afflicted individual "whether he had any spells today." The parents of many of our patients had made a routine practice of asking their children this question after they had been away from home for a period of time, such as attending school or some social function. This definitely is a harmful practice since it obviously keeps both the patient and/or his parents constantly conscious of the illness. We advise the parents to assume the attitude: "What they don't know won't hurt them."

THE PATIENT AND HIS ACTIVITIES

Rest. Many epileptic patients have the impression that they must get "plenty of rest" and also take naps during the daytime. Some patients informed us that their physicians instructed them to follow such a sleep pattern. This definitely is not the proper advice. The patient should be told that he does not need any more sleep than the average normal healthy person.

It is generally known that epileptic seizures frequently occur in association with sleep. There are two specific periods of the sleep cycle when they most often appear: (1) within the first 15 minutes to one-half hour after going off to sleep, and (2) one to two hours before the usual time of awakening. Many patients have their seizures only in association with sleep. These patients should be instructed not to take afternoon naps unless absolutely necessary.

Physical activity. The patient should be encouraged to participate in outdoor activities. Fresh air, sunshine, and physical activity generally have a favorable effect on epilepsy. Of course, the patient should be told that he should not perform activities such as climbing into high altitudes, horseback riding, etc. We allow our patients to go swimming, that is if they care to do so, but only under supervised circumstances, such as in the presence of a lifeguard or a competent buddy. We advise against diving or jumping into deep water.

Use of alcohol and tobacco. Some of our patients developed antisocial tendencies and a feeling of marked inferiority because they were told that they definitely should never "drink an alcoholic beverage." They were told that epileptics should not drink and also that alcohol and anticonvulsant medicine "do not mix." Many of these patients subsequently refused to attend various social

functions. They stated that it disturbed them considerably when they "couldn't join the crowd" in all of the activities of a party. It made them feel "different." We allow our patients to take a "social highball" if they care to do so. The decision is entirely up to them.

It is obvious that every individual should abstain from the excessive use of alcohol. The epileptic patient should be warned that this is particularly important in epilepsy. It is generally known that, in some instances, excessive alcohol precipitates seizures and also increases the sedative action of anticonvulsant drugs, particularly the barbiturates.

There is no medical proof, to our knowledge, that tobacco adversely affects the course of epilepsy. We have seen many epileptic patients who were forbidden to use tobacco in any form.

Intelligence of the epileptic. Some years ago it was an almost universal opinion of the general public and also of some physicians that all or at least most epileptic persons were or eventually would become mentally retarded or "insane."[7, 8] Even today many people have the impression that there is a definite relationship between mental retardation, and even insanity, and epilepsy. We inform our patients and/or their parents that this impression is completely unwarranted and that it stems from the time when there was no effective remedy for seizures. Epilepsy was then regarded as a hopelessly incurable condition. For this reason many patients with epilepsy were placed in institutions which housed mentally defective patients, idiots, and also other patients with many serious mental illnesses. One might as well believe in a relationship between genius and epilepsy as between mental retardation and epilepsy. Among the great men of history who are reported to have had epileptic seizures are Buddha, Socrates, Alexander the Great, Julius Caesar, Mohammed, Peter the Great, and Napoleon Bonaparte. Actually there is no consistent relationship between epilepsy and either mental retardation or genius. An epileptic person may possess other infirmities or he may be richly endowed.

We have not observed a statistically significant relationship between epilepsy and mental retardation. This fact should be emphatically emphasized to the patients and/or their parents since many of them are markedly disturbed, particularly the parents of normally intelligent children who develop epilepsy.

We have followed thousands of patients for many years and can definitely state that the vast majority of them maintained normal intellectual capacities. It is true that some individuals who sustain brain damage subsequently develop epileptic seizures. The question as to whether a convulsion per se causes irreversible brain damage is a controversial one. We believe that infrequent short seizures do not cause significant irreversible organic brain damage. On the other hand, it is our impression that prolonged major seizures or status epilepticus caused irreversible organic brain damage in some children.

Many epileptics in our experience have initially given the impression of low intelligence which was assumed to result from organic brain damage. However, after psychological testing of such patients it was concluded that the apparent low level of intelligence did not reflect their real status. In some instances, this apparent low level was due to emotional disturbance (because of the illness) and in others it was due to excessive medication. This problem should be investigated in each patient. The proper dosage of anticonvulsant medication for an epileptic patient is that amount which controls seizures without causing side reactions that interfere with general well-being. Most patients are better off having an occasional seizure rather than being seizure free with medication that causes them to be constantly dull and drowsy.

Education. Even in modern times, epileptic individuals are prohibited from attending many public schools and colleges merely on the basis of a diagnosis of epilepsy. This not only is unfair, but it is not

the attitude to assume with respect to any medical disability. The intellectual capabilities of each patient should be measured and decision in regard to school attendance should be governed accordingly.

Most of our school-age patients who have normal intelligence attend public schools and colleges and do well. Obviously the patient with frequent seizures (daily, weekly) could not, in most instances, be educated in a public school because of the frequent interruptions caused by seizures. However, it is important to note that this does not necessarily apply to patients whose seizures occur only in association with sleep. These individuals should be permitted to attend public schools. Educable patients with frequent seizures which occur during the daytime can obtain their education from home teachers or at so-called private hospital schools. The mentally retarded child with or without seizures will have to be sent to a special school for retarded children or to a custodial institution of some type.

We do not have significant difficulties with the schooling of children with infrequent seizures in our community at the present time. However, in the past we had considerable trouble. The difficulties generally did not stem from the administrative members of the school system, but from the teachers themselves. We were told by the school authorities that, in some instances, teachers absolutely refused to have an epileptic child in the classroom. Some teachers stated that the appearance of the seizures per se frightened them considerably, others expressed the fear that the child might hurt himself or even die as a result of a seizure. Some teachers said that their past experience with a seizure that took place in the classroom was that it disturbed some of the other pupils to the extent that they were unable to perform satisfactorily for the remainder of the school day.

Obviously the teacher's attitude, in many instances, stems from misconception and ignorance of the disorder of epilepsy. The physician can frequently clarify the problem by a personal interview with the teacher. If this is not feasible, he should relay his advice to the teacher via a school nurse or school counselor.

The teacher should be informed that the chance of severe injury resulting from a seizure is very minimal and that the chance of death is essentially nil. He should be told that, except for the word epilepsy, the "upsetting" effect of a seizure on the other pupils, if the situation is handled properly, should not be very different from that of a fainting spell, short temper outburst, or even a vomiting spell.

The teacher should first explain to the other students (in the absence of the patient) that the afflicted individual has a "disturbance" and that the seizure is a manifestation of his illness. He should also have a private interview with the patient to determine whether he is disturbed in any manner by the actions or attitudes of any of his classmates: whether they have refused to associate or play with him, called him "bad" names, etc. If no troublesome situations are apparent, the teacher should not continue with further discussions. However, in instances where the patient shows evidence of having been mistreated, the teacher should have another conference with the other students. In appropriate instances, he should define, in simple terms, the meaning of the term epilepsy; that is, of course, if this word has been mentioned. He should tell them to associate with the patient in the same manner as anyone else and explain that people with seizures are not "crazy," "different," or "peculiar" as has been expressed by many misinformed people in the past. It is obvious that the teacher should not call attention to these adverse designations unless they have been expressed by the classmates.

Training for the future. During childhood, plans should be laid for adulthood. Boys must acquire the training and education which are needed for a remunerative occupation. Girls generally need to acquire the many skills required to manage a household. It is the responsibility of the physician to see that advice on these matters is forthcoming.

Discussions concerning the patient's future vocation should be started at an early age so that he can adjust his scholastic training accordingly. We have found that generally the most appropriate time is during the first or second year of high school.

Employment. The epileptic patient faced with the problems of an occupation is likely to encounter difficulties. In many instances this is true even for patients who have been free of symptoms for many years. In fact, of all the common medical disorders, epilepsy is the only one where the name of the disorder frequently causes the patient more hardships than the disturbance itself. Cases 1 and 2 are illustrative of patients who were disqualified from employment solely because of a past history of epilepsy.

Case 1. About 5 years before we saw this patient, a 25-year-old male graduate civil engineer, he fell from a horse and for several months thereafter had a short "fainting spell" once or twice a month. His physician diagnosed his disorder as epilepsy and prescribed anticonvulsant medication. He was also classified 4F by the Armed Services at this time. He took the medication for 2 months and then stopped it of his own accord. For the subsequent 5 years he did not have the slightest indication of a spell and enjoyed perfect health. He was contemplating marriage and children, but was stymied in this respect because he was unable to secure employment. He said that he had been refused one job after another because of his 4F classification. He told us of one instance which disturbed him considerably. He made application for the position of civil engineer in a large company and was given an appointment for his medical interview. He was seated in the reception room and when it was his turn to see the medical director, the nurse called into the doctor's office, "Doctor, the epileptic is here to see you." He was immediately disqualified.

Case 2. A 26-year-old male had infrequent seizures up until he was 13 years of age. At 18 years of age he was drafted into the army and shortly thereafter was sent overseas where he participated in combat action for a period of 4 years. During this interval he did not have a seizure.

When he returned home, he obtained a job as an electrician at one of the larger establishments. After he had been working for several months and doing well, his foreman came to him one day and said, "Mister, I am sorry, but because of certain circumstances which we did not know about before, we will have to let you go." He went to the employment bureau where he learned that he was discharged because his employer learned that he was an "epileptic." He had not had a seizure for about 10 years and had served in the army on active combat duty for 4 years.

Problems of employment. Employment has to be considered in two different situations. The first is that of the individual who has never worked before; the other, that of the person who develops epileptic seizures after having been established in a vocation not suitable for an individual with seizures.

In the case of the first group (usually the younger individuals), if they are having seizures in spite of competent therapy, it is best that the physician assume that this situation will continue and prepare the child at an appropriate early age for certain possible restrictions as far as employment is concerned. The patient should be told that, in all probability, he will not be able to perform certain activities because of his disorder.

We have found that most patients are helped considerably when they are informed of this possibility several years or so before they reach the contemplated age of employment. They have sufficient time to reorient their way of thinking. As examples we mention 2 of our patients (sophomore high school students): one had his "heart set" on becoming an air force pilot and the other a surgeon. After several years of repeated discussions, these students were made to realize that they, in all probability, would not be able to go into these fields.

The second group (those who had been previously employed) frequently present a much greater problem. Many of them are

forced to change their employment. This may necessitate extensive rehabilitation and can cause the individual considerable financial and emotional difficulties. Some of our patients were helped with psychiatric guidance during this period of rehabilitation.

Sometimes these patients can be given encouragement if the physician mentions the names of outstanding individuals who were forced to change their employment because of disorders other than epilepsy. An excellent example is that of Roy Campanella, the major league baseball player, who became paralyzed in both legs as a result of an automobile accident.

We have found that the epileptic, at the present time, has considerable difficulty obtaining employment with the major industries. It is stated that "insurance problems" and compensation laws make the employment of "epileptics" prohibitive. We question whether this prohibition is based on actual statistical facts or on misunderstanding of the disorder of epilepsy.

The patient is more likely to secure employment in smaller organizations (out of sympathy or friendship in many instances) and most likely to obtain his financial livelihood from a vocation, profession, or business of his own. Table I gives a list of some of the occupations which are suitable and not suitable for patients with seizures.

There is no reason why an individual who is physically, mentally, and emotionally capable of working and has been free of seizures for a prolonged period of time should be disqualified from employment solely because he has epilepsy. Also, many of our patients with infrequent seizures are currently employed in various vocations and professions. They have performed their working duties in the same manner as a similar group of normal people. We have not been impressed with an accident rate any higher than would be expected in any other group of individuals. In fact, we believe there is good reason to predict a lesser accident rate among competent epileptics than among normal individuals. The sensible epileptic realizes his handicap and is therefore exceedingly cautious in performing his working activities, whereas the average worker frequently takes a more nonchalant attitude and performs automatic movements without "thinking."

Table I. Suitable and unsuitable occupations for patients with infrequent epileptic seizures

*Suitable**	
Farmer	Cabinetmaker
Gardener	Draftsman
Salesman (not requiring auto driving)	Jeweler
Clerk	Plumber
Mechanic (manually controlled equipment)	Forester
Laborer	Florist
Electrician (repairing or bench work)	Dog breeder
Technician	Photographer
Librarian	Physician (one who does not deal directly with patients)
Psychologist	Lawyer (one who does not participate in court activities)
Stenographer	Tailor (manually controlled equipment)
Veterinarian	
Accountant	
Unsuitable	
Surgeon	Those which necessitate altitude or ladder work
Those which necessitate operation of a motor vehicle of any type	Solitary watchman
Those which involve automatically controlled machinery or equipment	Swimming instructor or lifeguard
	Nursery maid

*Many of our patients are currently engaged in the various occupations designated as suitable and are performing well.

Automobile driving. Several states designate epileptics as a group who shall be denied the driving privilege categorically and by law.[9, 10] Most states, however, will allow an epileptic to operate a motor vehicle after he has been free of seizures for a period of time.

It is quite obvious that an individual with seizures should not drive an automobile. He must be told that he will have to conduct his activities without having this privilege. We believe, however, that there are exceptions to this blanket ruling. For example, an individual whose employment necessitates the operation of an automobile should be

allowed to drive if his seizures have always occurred in association with sleep. Also, a farmer with seizures should be permitted to operate a tractor or motor vehicle on his own property, if he cares to do so. The physician should explain to the farmer the calculated risk of injury to himself or his property. The patient should then make the decision himself.

A very important problem related to driving is that which is presented by the teenager. Many teen-agers who are not permitted to drive an automobile develop emotional disorders. It has been our experience that teenage psychological disturbances frequently can be prevented or at least minimized if the physician informs him about this restriction several years or so before he reaches the lawful driving age for his community. The child should be told that, in all probability, he will not be permitted to operate a motor vehicle. He should also be reminded periodically of this fact during his return visits to the physician.

The laws pertaining to epilepsy and driving vary somewhat from state to state. The physician or the patient should obtain this information from the proper authorities in his community. In the State of Maryland the general policy is as follows: After a patient has been free of seizures for at least three years, he is given his license. It is renewable for six month periods on recommendations of the attending physician and approval of the Medical Advisory Board of the Commissioner of Motor Vehicles, provided the applicant continues under treatment and has no seizures.

This policy has been in effect for many years in our state. Many of our patients are currently driving automobiles and, to my knowledge, the incidence of accidents in this group has not been any greater and is probably less than among the general population.

Marriage. Just as the problem of an adult occupation is important with boys, with both boys and girls there is the question, "Can I marry?" and "Is it reasonable to have children?" Certainly there is no reason for the epileptic not to marry. The emotional satisfaction of a home of his own has helped stabilize more than one patient. Of paramount and obvious importance, however, is the necessity that the prospective marital partner be fully aware of the situation. Physicians can do much by inviting both partners for a consultation in which all questions can be answered to the best of his ability.

The following question is natural, "What about our children?" In our present state of knowledge this is difficult to answer because no positive information is available. In dealing with the problem of inheritance with couples contemplating marriage, it is better to present the facts and leave to them the decision concerning the advisability of having children. This is a personal problem; some individuals would prefer a calculated risk rather than be denied the satisfaction of parenthood.

There are no reports in the medical literature which, in our opinion, prove that epilepsy is unquestionably an inherited disorder. In fact, we could not prove or disprove hereditary transmission of epilepsy from the results obtained in a recent survey made in our clinic.[5, 6]

We base our decision in regard to marriage and children primarily on the frequency of the patient's seizures and his or her physical and mental ability to raise a family. Obviously an individual who has frequent epileptic seizures would most likely be unable to care adequately for a family.

In spite of the fact that most authorities agree that the genetic factor in epilepsy is insignificant, there are ten states which forbid epileptics to marry and 18 which have sterilization laws applicable to epileptics. The laws of 14 of these latter states apply only to institutionalized epileptics.[9, 10]

Some of our patients have preferred to adopt children rather than take the slightest risk that their offspring may develop epilepsy. The following quotations from a letter from the executive director of a large charitable organization illustrate that the

"well-controlled" epileptic may encounter difficulties in regard to adoption.

"Our Medical Committee in considering adoptive applicants were concerned about their physical condition and were ruling out certain applicants on the basis of current or previous illness. . . . There was some discussion of epilepsy and it was the opinion of the chairman of our Medical Committee that any person who had had epilepsy in childhood, even though there might be no seizures present as an adult, should be ruled out. His thinking was that even though the child was 'supposedly cured,' there was certain emotional damage. . . . There were two of our Board members who have epileptic children and apparently have had considerable experience in dealing with their children's problems. They also had obtained a great deal of information about the illness and took marked exception to the recommendations of our chairman of the Medical Committee."

I believe that one could reasonably question whether an individual with active seizures, regardless of how frequently they recur, should be allowed to adopt a child. However, I can see no reason why a patient who has been completely free of seizures for many years should not be evaluated on the same basis as anyone else, that is, on his physical, mental, emotional, and financial ability to care for a child properly. The statement by the medical director of the adoption organization: ". . . even though the child was 'supposedly cured,' there was certain emotional damage," is definitely not true in my experience.

I have been in contact with hundreds of my patients who have been seizure free for many years and have not observed that their "emotional status" was any different from that of any other group of people. I do not believe that there is a specific syndrome, such as the "epileptic personality" which is mentioned so often in the older medical literature.

Injuries and longevity. Many patients live in a constant state of fear that they may injure themselves or even die as a result of a seizure.

As far as injuries are concerned, the patient must realize that there is a calculated risk of injury, particularly if he should be in a precarious position at the time of occurrence of a seizure. Those patients who have a well-defined aura can, in many instances, utilize this interval of time to protect themselves against injuries. This information should be carefully explained to the patient.

We have not been impressed with a significantly large number of accidents among our patients and question whether the incidence of accidents is greater with epileptics than among normal people. The intelligent epileptic realizes the nature of his disorder and is usually exceedingly cautious when performing actions such as walking across the street and other activities which require that he be on the alert. Also, he does not do such things as drive an automobile, go swimming alone, or climb to high altitudes, etc.

As far as longevity is concerned, the physician can definitely tell his patient that epilepsy per se rarely, if ever, causes death and that there is no reason why he should not live "as long as he would if he did not have epilepsy." I give many of my patients encouragement by telling them that sometimes it is "good" for the person to have a "minor handicap." Many such individuals take better care of themselves and do not take unnecessary risks. Many handicapped people live a healthier, longer, happier, and more productive life than "perfectly" normal people.

CONCLUSION

In conclusion, it should be reiterated that although we have presented some of the pertinent difficulties of the epileptic patient, these problems vary from patient to patient. The physician who is well oriented in regard to the disorder of epilepsy can do no better than ask himself, "What would I do if this were my child?" and advise the patient and/or his parents accordingly. There is no substitute for a realistic attitude which accepts each patient as a person with a certain degree of handicap, but with potentialities which are to be encouraged to the utmost.

The doctor's attitude will be reflected in the ability of the parents and friends to accept the patient as an individual rather than as a stereotyped "epileptic." Failure in this respect may mean failure in the rehabilitation of the patient.

SUMMARY

1. Some of the significant problems which the epileptic patient encounters, such as difficulty in securing employment, proper education, and the like, are presented and discussed.

2. Recommendations and advice which the physician can offer to the patient in order to assist him in coping with his difficulties are presented.

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor

Gordon F. Vawter, M.D., Assistant Editor

Case 1. This 9-year-old girl was referred to The Children's Hospital Medical Center following biopsy of a lesion of the left knee. The patient first noted discomfort in the left knee about one month before admission. This began after she caught herself and twisted the knee while going down some steps. She did not fall or bump herself. The pain persisted on the medial side of the knee and required 300 mg. of aspirin 5 times per day for relief. She was able to walk, with slight difficulty, until 2 weeks before admission. There was no redness or heat. Increase in swelling and in pain just below the knee joint prompted an x-ray examination. This showed periosteal elevation or soft tissue calcification along the cortex of the medial metaphyseal portion of the tibia, approximately 1 cm. below the epiphyseal plate (Fig. 1*A*). A biopsy was performed and the child was sent here for further study and treatment. There had been abrasions and contusion in the area 10 months before, following a fall on the left knee.

On admission here, physical examination was normal except for limitation of motion of the left knee, because of pain and marked swelling and some ecchymoses about the site of biopsy which had been performed 5 days previously.

Blood contained hemoglobin, 11 Gm. per cent; white blood cells, 17,000 per cubic millimeter with 69 per cent polymorphonuclear leukocytes; calcium, phosphorus, and alkaline phosphatase were normal. Urinalysis was entirely negative. X-rays were taken.

Case 2. This 5 10/12-year-old girl was admitted for evaluation and treatment, with the following history:

Six weeks prior to admission she fell and scraped her left shin. Persisting tenderness over the area of the proximal tibial plateau and pain on weight bearing prompted an x-ray 1½ weeks after the injury. A tentative diagnosis of fracture of the tibial plateau was made, although no abnormality was seen on the x-ray. Despite the use of crutches, the symptoms persisted and 1½ weeks later a second x-ray showed irregular radiolucency in the upper tibia with slight periosteal calcification (Fig. 2). One week later she was admitted to the hospital for study.

The past history was generally negative but does include diagnostic x-rays of the mother during pregnancy, at term. There is a family history of diabetes, allergy, and cancer.

Examination revealed a pale, well-developed, and well-nourished child with normal vital signs. Physical examination showed

only slight swelling and tenderness over the left tibial plateau. There was no local heat or discoloration. Apart from slight limitation in motion of the left knee, there was no limitation of motion in other joints.

Urinalysis was essentially negative. Blood studies showed a hematocrit of 38 per cent, a leukocyte count of 5,900 per cubic millimeter, with 20 per cent lymphocytes, 10 per cent monocytes, 4 per cent band forms, and 66 per cent segmented polymorphonuclear leukocytes. The sedimentation rate was 22 mm. per hour, uncorrected.

A biopsy was performed.

DR. ARTHUR W. TROTT.* I would like to emphasize certain similarities in these two children. Both are girls, both are in the first decade of life, both have a lesion of the bone on the medial side of the proximal metaphysis of the tibia, and both have a history, dating back 4 to 6 weeks, of tenderness or discomfort in the area of the lesion. There were pain and swelling but, remarkably enough, neither one had other evidence of infection, such as local heat or fever. Congenital syphilis would have been apparent before this. Tuberculosis has a longer history, does not usually behave in this way, and will show other areas of involvement, such as the lung. Also, in tuberculosis of the bone at this age there is usually tuberculous synovitis as well, for which there is no evidence in these patients. Both of these children had a history of trauma to the area. In the first patient there was a twisting injury, and in the second there was a fall with a scrape of the shin. Almost any child with a lesion of bone will have a history of trauma if one searches for it, and the biggest problem is to relate the trauma to the particular lesion. Laboratory studies offer little outside of mild anemia and leukocytosis in the first patient. Perhaps the leukocytosis reflects the biopsy 5 days previously, rather than infection.

In the second patient, the sedimentation rate is elevated but the white blood cell count is normal. The laboratory findings help very little. By x-ray both children have a defect in the bone of the metaphysis characterized by destruction of the cortex and the presence of subperiosteal new bone. The general metabolic diseases can be eliminated since the children are generally well, and one might well expect the diseases to become manifest before this time, although there are some that might develop even later.

We have to think of trauma. There is only about one type of lesion which would fit into this picture of recent trauma, and that is a myositis ossificans or periosteal bone formation secondary to trauma. The one thing against myositis ossificans in these two children is that there is destruction of the cortex where the lesion exists, whereas, usually in myositis ossificans, new calcification lies in close proximity to, but outside of, the bone. The cortex is not usually involved, so I do not think that these represent traumatic lesions. However, we must remember that the first patient had a biopsy. Acute osteomyelitis does follow episodes of trauma

A *B*

Fig. 1*A*, Case 1. Postbiopsy x-ray showing soft tissue swelling, appearance of periosteal elevation, and defect of cortical bone with retained underlying trabecular pattern.

Fig. 1*B*, Case 1. (Two months later) Calcification along margin of reaction gives a cystlike pattern. There is no progression of changes in bone proper.

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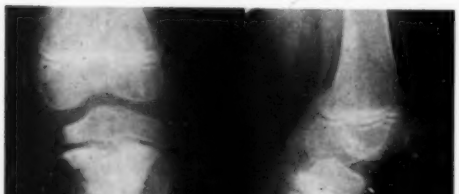

Fig. 2. Case 2. Periosteal elevation and moth-eaten radiolucence from destruction of bony metaphysis are noteworthy.

(usually fairly soon), but there should be more signs of infection. Occasionally, with the advent of antibiotics, a rather peculiar story and picture with osteomyelitis is present where antibiotics have been given but not in sufficient quantity to eliminate the infection. There the destruction of bone smoulders along, will tend to evacuate itself through the destroyed cortex subperiosteally, and might possibly produce some of the x-ray findings described here. The laboratory data, physical findings, and lack of fever do not fit in these instances. There are many destructive lesions of bone by tumors which can occur in this area.

Among benign lesions, the aneurysmal bone cyst is a slowly growing one which usually begins in the metaphyseal area, but this is expansile, has a cystlike appearance, pushes the periosteum out, and there is a thin layer of new periosteal bone laid down as the lesion expands, so as to give a soap-bubble appearance in the ends of long bones. Symptoms usually occur late, often after pathologic fracture. Other lesions are fibrous defects of bone or aclasial defects, but these are usually symptomless. Fibrous dysplasia does occur in metaphyseal areas, often accompanied by cafe-au-lait spots or some other abnormality but is usually asymptomatic unless there is marked bone deformity or complicating fracture. Osteoid osteoma is found in this age group and may occur in the locations described here. The history of either of these cases is not long enough for an osteoid osteoma since, by and large, the history extends over a period of months and, in fact, it may take a period of 3 to 6 months before characteristic changes by x-ray occur. Usually there is no destruction of the cortex but rather proliferation of new bone with a lot of osteoid tissue, and I do not think the x-rays fit in with this picture at all. Hemangiomas (and hemangiosarcomas) do occur, but they are rare tumors, particularly in the long bones. They usually are quite extensive before symptoms are produced. The very interesting "benign osteoblastoma" has, as far as I know, not been described in this age group. There is another lesion associated very closely with the osteoblastoma, and that is the benign chondroblastoma. It is a tumor arising from the chondroblasts at the epiphyseal plate or in the area; it is usually located in the epiphysis but does extend into the metaphyseal area giving a lytic defect with marginal sclerosis; it is a slowly growing lesion and, therefore, does produce reaction on the part of the surrounding bone, but like most tumors of cartilage, areas of calcification are amorphous; often these lesions are purely lytic. Growth of this lesion is slow and again it is usually found in adolescence, often in the proximal humerus.

In children of this age group there is a benign lesion whose nature or existence is controversial. That is the chondromyxofibroma. It contains cartilage, myxomatous tissue, and fibrous tissue. It is found in the metaphysis and is usually eccentric in position as these lesions were. It is a relatively rare lesion, but it does produce, quite frequently, a thin line of reactive bone around the lesion, and it may expand to elevate the periosteum and produce new bone. If it gets large enough to weaken the bone and produce pathologic fracture, then one finds callus formation which may obscure the picture. This callus formation, under the microscope, may resemble an osteogenic sarcoma so that it does cause confusion at

times. However, this is a slowly growing lesion with which there is a long history of difficulty; the pain is usually not very severe, but there is overlying tenderness.

That leaves us with malignant lesions in which there is a survival rate, even at the lowest, of between 10 and 20 per cent over a 5-year period, so it is important to act quickly if necessary. We can eliminate fibrosarcoma, since it does not produce bone. It is usually found in an older age group as a slowly growing tumor, whose average duration of symptoms before diagnosis is around 20 months in most series, and again the chief symptom is pain, as it is with most of these malignant tumors of bone. The reticulum cell sarcoma is a fascinating lesion which does occur in children but is most common in adolescence. It causes destruction of bone in this patchy manner, but it may give a solitary lesion which erodes the cortex, expands rapidly, destroying bone as it goes, usually without too much in the way of bone reaction to it. Some osteoblastic proliferation may be with this tumor, and one can find x-ray pictures of the tibia in this particular type of tumor which resemble the x-ray pictures (which we will look at shortly) of this second girl. However, there may be multiple lesions rather than a single big lesion. Synovioma or synoviosarcoma is a rare tumor; it is a slowly growing one and usually invades bone from the outside rather than originating in bone.

Of the two major and more common malignant tumors of bone that we have to deal with, one is Ewing's sarcoma. The greater incidence of Ewing's sarcoma is in the first decade, at least in our series. With Ewing's sarcoma there frequently is fever, pain, elevation of the white count, and the sedimentation rate. The only thing against the Ewing's tumor in these children is that the most common site of origin for Ewing's tumor is the central portion of the shaft of the bone; it usually occurs in the marrow cavity at the midpoint of the shaft, rather than at either end. When it does occur in the end, it may give rise to more new bone formation than it does in the shaft, but one sees extensive involvement of a spotty and more or less discontinuous nature up and down the shaft. In these initial x-rays there is no evidence of that. The characteristic appearance by x-ray is the so-called "onion-skin appearance" which is due to laminated layers of periosteal new bone formed as a result of the expansion of the tumor, but

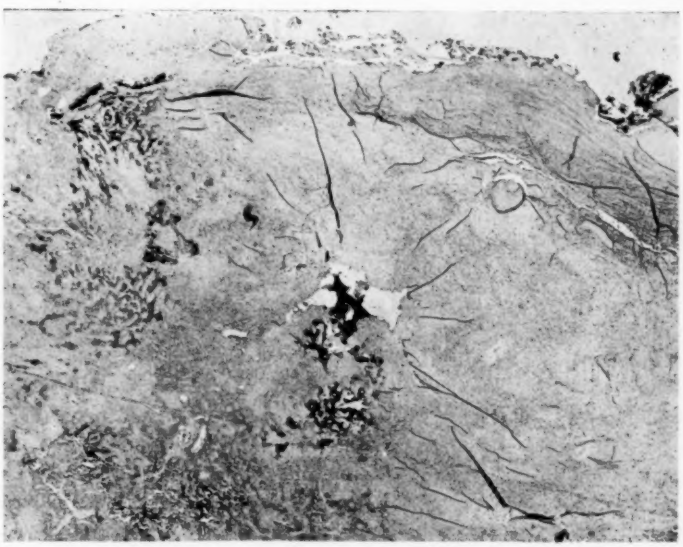

Fig. 3. Case 1. The general topography of the biopsy with "periosteum" at the top shows the cellular center and irregular marginal ossifying and calcifying structures. (Hematoxylin and eosin. Original magnification ×10.)

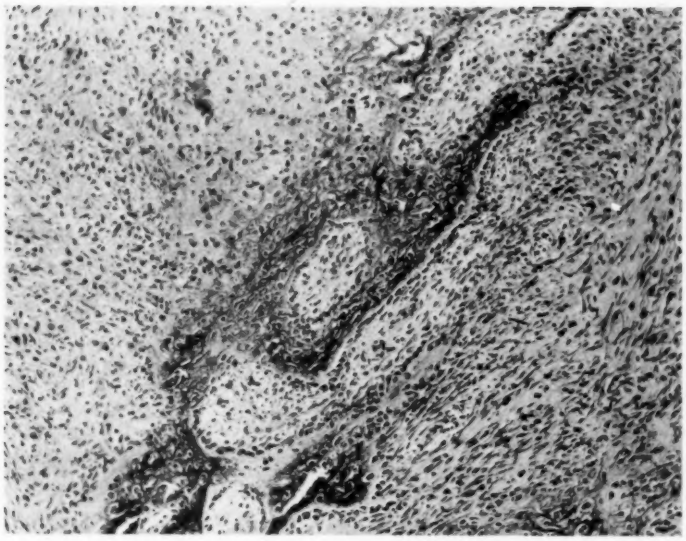

Fig. 4. Case 1. Active spindle cell proliferation and variable stages of osteogenesis and callus-like formation are seen. (Hematoxylin and eosin. Original magnification ×375.)

other tumors of bone sometimes show this finding. Occasionally, Ewing's tumors present the "sunburst" x-ray pattern usually seen in osteogenic sarcoma. Each of these tumors can show the triangular area of periosteal new bone formation at the margin of the tumor, known as Codman's triangle. This triangle is produced by tumor invasion at that point with erosion of the newly laid-down bone, but it is not characteristic of Ewing's and is found in osteogenic sarcoma and other tumors which expand and raise the periosteum.

On the basis of location and certain other features I do not think that either one of these children had a Ewing's tumor, although when Ewing's tumor and osteogenic sarcoma occur in the metaphyseal region they may have a very similar x-ray appearance. Osteogenic sarcomas arise predominantly in the metaphyseal area where the most active bone growth and remodeling occur; in fact, 75 per cent of these highly malignant tumors occurs about the knee, usually in the distal femoral metaphysis. These tumors usually arise within 5 cm. of the epiphyseal plate. Pain is usually present, we think, because of rapid expansion with destruction of bony cortex and formation of a large soft tissue mass with elevation of the periosteum. If a great deal of bone is being formed by the tumor cells, the serum alkaline phosphatase may be elevated. Some of these tumors are primarily osteolytic, but, characteristically, the sunburst x-ray may be seen in osteoblastic tumors where new bone is being laid down subperiosteally in columns perpendicular to the axis of the long bone.

Now in the first patient the x-ray shows some destruction of the cortical bone on the medial side, possibly in part related to the previous biopsy. Since the x-ray films suggest that the lesion may be active between cortical bone and periosteum without destruction of the bony trabeculae within the bone, we must consider a rather unusual tumor, known as parosteal osteogenic sarcoma. As the name indicates it seems to develop along the outer surfaces of the bone. There is some controversy as to whether this is a true entity, clearly separable from ordinary osteogenic sarcoma or not. The lesion tends to progress slowly, and some have considered it to be initially benign, with malignant transformation occurring later. The lesion is not radiosensitive but excision of the area has been successful in some cases. Lichtenstein[1] has described such a lesion,

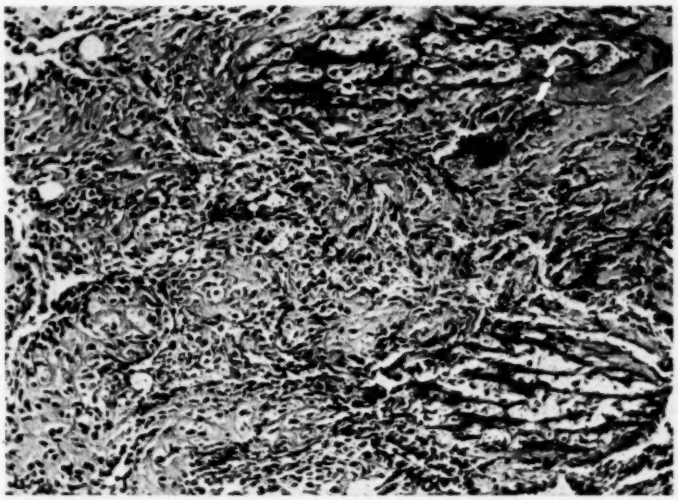

Fig. 5. Case 2. Sarcomatous elements are intermixed with abnormal cartilage and bone to represent osteogenic sarcoma. (Hematoxylin and eosin. Original magnification ×325.)

very closely resembling what we see here, in a 5-year-old girl, although it ordinarily occurs in an older age group.

If we look at x-rays of the first patient taken 1 or 2 months later, we see that there is no progressive destruction of the bone proper, but a thin shell of calcification has been formed along the outer rim of the soft tissue mass, the centers remaining undermineralized (Fig. 1*B*). As we follow the lesion along, this pattern continues with no apparent increase in size. This behavior is, I believe, quite compatible with parosteal osteogenic sarcoma.

In the second case, on the other hand, there is definite destruction of the bony

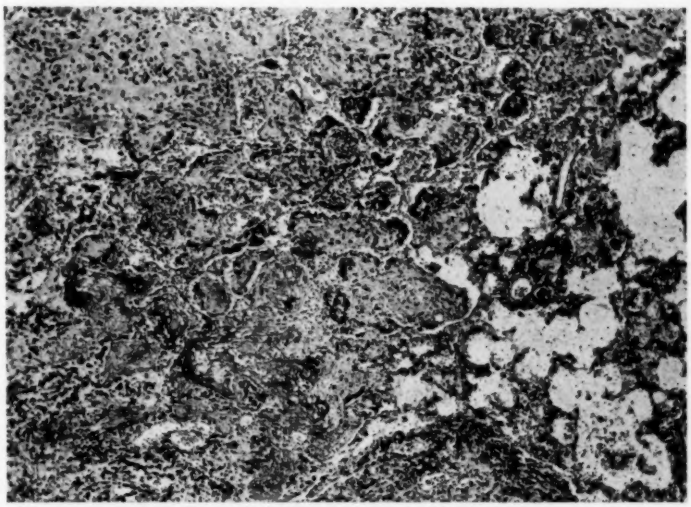

Fig. 6. Case 2. Metastasis of osteogenic sarcoma in lung at autopsy resembles the biopsy. (Hematoxylin and eosin. Original magnification ×90.)

pattern within the metaphysis, giving a pattern of osteolytic growth, although there are a few tiny areas of fuzzy sclerotic bone, perhaps representing reaction or degeneration rather than tumor osteogenesis. Periosteal new bone is evident outside the tumor. I have very little doubt that this lesion represents an osteogenic sarcoma, which is predominantly destructive.

DR. GORDON F. VAWTER. Would either of these lesions be compatible with a metastasis, say from a neuroblastoma?

DR. TROTT. I think this is unlikely, since most metastatic lesions tend to be lytic with a punched out radiolucency and relatively little reaction.

DR. CHARLES A. JANEWAY. How can one exclude inflammation so completely?

DR. NEUHAUSER. I do not think any one of us, clinician, radiologist, or pathologist can feel absolutely sure of occasional lesions. One of the things we were impressed with in the first case was the marked soft tissue swelling when first seen, followed by a sudden outpouring of calcium salts. This reminds me of a case presented at a recent Penrose Clinic Cancer Seminar where all of the pathologists made a diagnosis of myositis ossificans, whereas all of the radiologists had offered a diagnosis of osteogenic sarcoma. Occasionally, the disagreement is so strong that we have to watch the patient to see what will happen.

DR. VAWTER. In the first case uncertainty attended our interpretation of a beautifully prepared and quite adequate biopsy sent in from the referring hospital. Ultimately, several pathologists around the country were good enough to look at the material. The final tally was in favor of *myositis ossificans*. Pathologically, there was a proliferative center with active spindle cells almost sarcomatous in appearance. Around the outer margin there was extensive maturation of connective tissues and moderate calcification; sometimes the pattern suggested fracture callus, in part (Figs. 3 and 4). No great destruction of cortical bone had occurred. This pattern of central proliferation and marginal differentiation is one of the characteristics of myositis ossificans and of a related lesion, traumatic periostitis. If one has a biopsy only of the central part during its active phase, one is very prone to suggest the diagnosis of sarcoma. This inner and outer pattern, too, seems to be related to the fact that as many of these lesions progress they form a peripheral shell of radiodense calcification in much the way that this patient did.

DR. PAUL P. GRIFFIN. I hope the pathologists are correct in their interpretation, since this child was originally sent to us with a diagnosis of osteogenic sarcoma. Anyway, we have decided to follow this lesion and so far it is behaving in just the way one would expect that myositis ossificans would behave, and we have now followed her for over a year. One thing that impressed me was the marked amount of pain this child had, more than is usual, perhaps, for osteogenic sarcoma.

DR. VAWTER. In keeping with the frankly destructive lesion in the second child, the biopsy specimen consists of a densely cellular sarcoma showing rather little tendency to form osteoid matrix: the lesion is clearly an *osteogenic sarcoma* (Fig. 5). Also in keeping with this diagnosis, the tumor spread rapidly through the bone locally and soon there was evidence of metastasis to a vertebra and to the lungs, with fairly rapid progression over a period of several months, to a respiratory death (Fig. 6).

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COMMENTS ON CURRENT LITERATURE

Chromosomes in chronic myeloid leukemia and in acute leukemia associated with Mongolism

THE simultaneous occurrence or possible association of Mongolism and leukemia was discussed by Ingalls[1] as early as 1947 in a report concerned with the pathogenesis of Mongolism. Two Mongoloid children in a series of cases reviewed by Ingalls died of leukemia, one an infant 8 weeks of age who died of "acute myelogenous leukemia," and the other a child who suffered from "acute lymphatic leukemia" with fatal outcome at the age of 19 months. During the ensuing 10 or 12 years, the simultaneous occurrence of Mongolism and leukemia was recorded in a number of instances.[2] A survey of neoplastic disease in childhood was carried out in 1958 by Stewart, Webb, and Hewitt.[3] Mongolism was found in 17 cases among the 677 children with leukemia, and in only one of the 739 children with other neoplasms.

The discovery of an extra chromosome in Mongolism by Lejeune, Gautier, and Turpin[4] in 1959 was corroborated very shortly by Jacobs and her colleagues,[5] and by Böök, Fraccaro, and Lindsten.[6] A year previous to these publications Jacobs and her co-workers[7] had emphasized the association between Mongolism and leukemia and the karyotype abnormalities which were being described in some cases of leukemia. These authors stated that leukemia offers a special opportunity for serial chromosome studies permitting correlation between chromosome abnormalities and clinical type and behavior of the disease. At the Second Symposium on Nuclear Sex held in London in September, 1959, a member of this Edinburgh group of investigators, W. M. Court-Brown,[8] described cases of aneuploidy in leukemia and reported upon a patient with Mongolism and leukemia in whom the verified chromosome number was 47, the extra chromosome being the small autosome, pair 21 (Denver classification), which is considered characteristic of Mongolism.

Early in 1960 Nowell and Hungerford[9] reported the finding of a chromosome anomaly in 2 cases of chronic myeloid leukemia, which was designated by them the Ph^1 chromosome from their location, Philadelphia, in accordance with the recommendations on nomenclature of abnormal chromosomes at the Denver conference.[9] On further study this observation was substantiated by the authors[10] and was verified also by members of the Edinburgh group of investigators.[11] In all these instances it was noted that the chromosome number was normal (46), but that there was a morphologic abnormality of one of the small acrocentric autosomes causing this particular chromosome to appear unusually small. Apparently this small Ph^1 chromosome is not an extra chromosome, as in Mongolism (47 chromosomes), but one of the 4 small autosomes (pairs 21 or 22 which are difficult to

distinguish) with about one half its substance missing. Recognition of such an abnormality in a human chromosome demands cell preparations of a quality possible only recently with the newer developments in blood cell tissue culture methods, and in the cytologic technique for the study of chromosomes.[10] Bone marrow tissue culture employed earlier in chromosome studies did not reveal the finer morphologic detail of the human karyotype. The Ph^1 chromosome was seen in blood cell preparations from all 7 of the cases of myeloid leukemia reported by Nowell and Hungerford[10] and in 12 of 15 uncomplicated cases encountered by the Edinburgh group.[11] Careful studies concerned with the proportions of cells containing the Ph^1 chromosome in blood cell cultures from the various patients indicate that only the actual leukemic cells are involved. The chromosomal pattern was found to be normal in cells of skin-biopsy cultures from these patients and in normal cells of the blood.[11] Thus the Ph^1 chromosome abnormality is not considered to be an inherent chromosome anomaly present in all of the patient's cells, as is thought to be the case in Mongolism, but a defect intimately associated with the development of leukemia, possibly a somatic mutation in some of the patient's leukoblastic cells. Loss of substance by this small autosome may represent deletion only or it may involve transfer of chromosomal substance to another chromosome by translocation. Gain of a small amount of chromosomal material by one of the larger chromosomes of man would be more difficult to detect than its loss from one of the smaller chromosomes.

Two very interesting reports in this investigative field have appeared recently which deal with cytogenetic studies in chronic myeloid leukemia and in acute leukemia associated with Mongolism. One of these reports by Alan W. Johnston[12] concerns a boy 3 years of age when first admitted to the hospital because of acute leukemia. His development had been retarded from birth, and the child showed the typical characteristics of Mongolism, including Mongoloid facies with epicanthic folds. The father was 40 years of age at this time, the mother 39 years; 2 male siblings, aged 11 and 15 years, were normal in all respects investigated. Inquiry into the family history revealed that 2 persons in the collateral relationship, both males, had died of leukemia, one at 23 years of age and the other later in life. Both bone marrow tissue cultures and blood cell cultures were followed in this child. Cultures obtained before treatment particularly were studied in detail for chromosome changes. The chromosome number was 47 with the trisomy that of pair 21, characteristic of Mongolism. Leukemic cells in the blood cultures showed abnormalities of the chromosomes, chiefly fragments and breaks. Treatment in this child by the administration of a folic acid antagonist resulted in a clinical and hematologic remission. Blood cell cultures taken during remission showed 47 chromosomes with no chromosomal fragmentation.[12]

The other recent report is by the Edinburgh group of investigators[13] and describes chromosome studies of blood cell cultures from 18 patients with chronic myeloid leukemia, 3 of whom passed into the acute phase. In 13 of the 18 patients an unusually small acrocentric chromosome was observed with regularity in leukemic cells, and was identified as the Ph^1 type of chromosome. These authors report, in addition, the results of chromosomal studies employing the same blood cell culture technique in 5 patients with acute leukemia associated with Mongolism. Among the patients studied the authors encountered also one case of sex mosaicism of the XY/XXY type, and one patient with acute leukemia in whose cell cultures the second stem line of cells was characterized by a chromosome count of 49. In the 5 patients with acute leukemia and Mongolism, the chromosome configuration (47 chromosomes) was that associated with Mongolism, the additional chromosome being the small acrocentric autosome considered characteristic of Mongolism. These authors conclude that the majority of cases of chronic myeloid leukemia is associated

with the Ph^1 type of chromosome, and that in some cases of Mongolism there is an increased disposition toward the development of acute leukemia, with or without chromosomal fragmentation in the leukemic cells.

The Ph^1 chromosome has been reported only in chronic myeloid leukemia, and apparently it is present in the majority of such cases of leukemia. However, as has been emphasized by a number of investigators, it does not follow that this chromosomal change accounts for the etiology of chronic myeloid leukemia. Prior to the discovery of this Ph^1 deletion or translocation, control of leukopoiesis had been postulated on the basis of a circulating inhibitor or deficiency of such an inhibitor, with the possibility that certain definite genetic loci on the chromosomes are concerned with leukopoiesis.[14] In an attempt to correlate some of the observations and postulations concerning this problem, the Edinburgh group has suggested a working hypothesis based on the following points:

1. "On present evidence the majority of cases of chronic myeloid leukaemia is associated with the Ph^1 chromosome.

2. "The Ph^1 chromosome is an abnormal small acrocentric chromosome (either no. 21 or 22, Denver classification) formed as a result of a deletion or a translocation.

3. "Mongols (47 chromosomes) are either trisomic, or effectively trisomic, for a small acrocentric chromosome believed to be no. 21.

4. "Mongolism is associated with an increased disposition towards the development of acute leukaemia."[13]

The authors state in conclusion: "For purposes of argument it may be postulated that a locus exists on the chromosome involved in mongolism which is in some way concerned with leucopoiesis, and it will be assumed that this chromosome is no. 21. If the postulate is extended to include the suggestion that the same chromosome is involved in chronic myeloid leukemia as in mongolism, then two conclusions follow: firstly, triplication of the locus is associated with an increased liability towards acute leukaemia; and secondly, either a deletion or a translocation involving the locus is associated with most cases of chronic myeloid leukaemia."[13] These authors stress the potential value of cytogenetic studies in an understanding of leukemia, and other clinical conditions in which changes in chromosomal pattern might be concerned, calling attention particularly to the need for close correlation between the clinical syndrome in all its phases and the cytogenetic deviations observed.

Interesting as these investigations are, it must be emphasized that cytogenetics is at best a very complex field of study, and that the technical aspects are difficult; irregularities may be inherent in some of the procedures, and even with the experienced investigator artifacts may lead to false conclusions.

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Books

For Young Adults Only; The Doctor Discusses Your Personal Problems.

Frank Howard Richardson, M.D., F.A.C.P., F.A.A.P., Atlanta, 1961, Tupper & Love, Inc., 133 pages. Price $2.95.

Twenty-one brief chapters on such subjects as dating, petting, drinking, smoking, safe driving, making friends, and so on—as books of advice to young people go, this is a good one, sensible, understanding, succinct, although of course a little corny. Like other books of its kind, it will surely have very slight appeal to the oversophisticated or rebellious teen-ager, or to the sensation-seeking hot-rodder, for instance. It will not reach those who most need it, or those whose parents most need it. It is aimed at the child already well supplied with good advice; and indeed it is very little different from the generality of books in this field, whether written by doctors, ministers, or teachers. The subtitle is accurate but misleading. To this reader it is matter for regret that the respected author of this book chose to include very little medical information, and that somewhat watered down. Young adults, like older ones, respect medical information, and resent having it too much diluted.

L. M. HOLLOWAY, M.S. IN L.S.

Dietary Protein in Health and Disease.

James B. Allison, and William H. Fitzpatrick, Springfield, Ill., 1960, Charles C Thomas, Publisher, Price $4.50.

This book is an admirable illustration of the saying that "good things come in small packages." It is a compact account of some of the major problems in protein nutrition and is presented in a delightfully clear and succinct fashion.

No one is (or should be) more directly concerned with the human requirements of protein and amino acids than the pediatrician. In spite of this, he too often offers advice beyond his knowledge of this subject.

This "small package" represents an ideal starting point for the acquisition of knowledge in this often-misrepresented field.

DANIEL FLEISHER, M.D.

Die Odeme: Physiology and Therapy of Salt and Water Retention.

Jean Fabre, Basel, 1960, B. Schwabe & Co., 304 pages.

A French edition of this book was published in Paris in 1959; it is the German edition, issued in collaboration with Dr. Andreas Fanconi and R. Martin Rothlin, which is reviewed here. By reason of his extensive work in the field of edema, electrolyte and water metabolism as a member of the medical faculty of the University of Geneva, Dr. Fabre is thoroughly at home in his field. Like most German medical publications, this book is outstanding in its excellent format and illustrations.

It is divided into three parts. The first part, which deals with the physiology of electrolyte and water metabolism, is thorough and easily read. Fabre assumes here that the reader needs to be introduced to the basic principles of physiology and chemistry in this field. The hormonal regulation of water retention and the effect of salt administration on water retention are carefully discussed. The physiology of aldosterone production and action, and the relationships of intra- and extracellular water compartments to electrolyte concentrations are competently treated.

The second part discusses in 14 chapters the pathologic physiology of edema. The third part, in 8 chapters, deals with the treatment of edema. In great detail, Fabre discusses the use and mechanism of action of salt-free diets, exchange resins, diuretics, steroids, artificial kidneys, and other means of treatment.

For workers in this field, the extensive bibliography of 960 references from French, German, and English literature should be of special value. Swiss specialists, who of necessity acquire facility in many languages, render a real service in acquainting others with the international literature in their fields.

WALTER HEYMANN, M.D.

Correspondence

To the Editor:

Cytogeneticists are no doubt aware of the vast numbers of chromosomal aberrations possible in man. Others (especially pediatricians, who may be most directly concerned) may find the figures surprising.

Since there are 22 autosomes, there are of course only 22 possible simple trisomics. Multiple trisomics (having 2 or more chromosomes present in triplicate) and monosomics (lacking one chromosome of one or more pair) occur; in fact, it would appear that multiple trisomy and monosomy can coexist.[1] The existence of an individual with complete autosomal triploidy and an XXY sex chromosome constitution[2] indicates that relatively great abnormalities of karyotype may be compatible with survival.

The number of combinations of n different things taken r at a time is:

$$ {}_{n}C_{r} = \frac{n(n-1)\ (n-2)\cdots(n-r+1)}{r\,!} $$

Thus, although there are only 22 autosomal trisomics of first degree, there are 231 possible double trisomics, 1,540 triple trisomics, 7,315 quadruple trisomics, etc. The sum of all possible trisomics in man is:

$$ \sum_{r=1}^{r=n-1} {}_{n}C_{r} = 2^{n} - 2 $$

or more than 4 million. There is an equal number of possible monosomics, though perhaps relatively few of these will be found to be viable.

Combinations of trisomy and monosomy in the same individual run into astronomical figures. The calculation is that for the "two-draw" problem in permutations and combinations. If r_k is the number of trisomic chromosomes in a given individual, any combination of the remaining $(n - r_k)$ chromosomes may be monosomic. The number of possible combinations of the remaining chromosomes is:

$$ \sum_{r'=1}^{r'=n-r_k} {}_{n-r_k}C_{r'} = 2^{n-r_k} - 1 $$

Since the number of trisomic combinations of r_k chromosomes is:

$$ {}_{n}C_{r_k} = \frac{n(n-1)\ (n-2)\cdots(n-r_k+1)}{r_k\,!} $$

the total number of tri- and monosomic combinations possible for the condition r_k = the number of trisomic chromosomes is:

$$ \frac{n(n-1)\ (n-2)\cdots(n-r_k+1)}{r_k\,!}\left\{2^{n-r_k} - 1\right\} $$

To obtain all possible combinations of combined tri- and monosomy, the above expression is summated from $r = 1$ to $r = n-1$. If $n = 22$, the total is more than 31 billion.

This number is increased several fold by considering abnormalities of sex chromosome consititution. If autosomal tetrasomics and higher degrees of polysomy and polyploidy exist, the figures become even more staggering. Mosaicism and abnormalities involving portions of chromosomes (deletions, duplications, inversions, and translocations) provide a number of possible variations that is for practical purposes infinite.

These calculations, which are based on elementary algebra, are presented without any claim to originality or priority, simply in the belief that they will be of interest to pediatricians. They show that the category of the karyopathies is one of vast dimensions. Although little is known about the viability of severely aberrant karyotypes, it may be expected that the future will bring an ever-increasing flood of reports of abnormalities of chromosome constitution.

JOHN C. GALL, JR., M.D.

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To the Editor:

Dr. Gall's calculations are indeed interesting, and the total number of mathematically possible combinations is staggering. However, these calculations have little meaning in the physical world. While more chromosomal abnormalities will undoubtedly be found now that the intensive search is on, the sum total will be sharply limited, as can be appreciated from a number of considerations. The vast majority of chromosomal deletions are undoubtedly lethal. The number of translocations and duplications are limited by as yet not fully understood relationships governing the inter- and intra-actions of chromosomes during nuclear division. Furthermore, the total number of syndromes known (or even hypothecated) which involve more than one gene abnormality (i.e., multiple system defects) is, conservatively speaking, numbered in the tens or hundreds, not in the millions or billions. One need not postulate the existence in the world's human population of a greater number of karyotypes than there are phenotypic abnormalities to explain, or for that matter, individuals. Indeed the list of diseases in which karyotypic abnormalities have been sought for and not found is growing faster than the list of proved chromosomal abnormalities. While theoretical considerations such as those presented by Dr. Gall are intellectually stimulating, they should not be misconstrued to imply that with the advent of the technique of chromosome counting a new and hitherto unseen Pandora's box of diseases has been opened.

VICTOR H. AUERBACH, PH.D

*News and notes**

The **Third Symposium on Cinefluorography,** originally scheduled for the spring of 1961, has been postponed to Dec. 1 to 2, 1961, it has been announced by Dr. Stanley Rogoff, Division of Diagnostic Radiology, University of Rochester Medical Center, Rochester 20, N. Y. Program includes orientation in problems of motion picture radiography and demonstrations of the application of cinefluorography; scientific papers on these and allied subjects are invited. Registration is limited to 150; applications and inquiries may be addressed to Dr. Rogoff.

The first **All Asian Congress of Pediatrics** was held in New Delhi, Jan. 2 to 6, 1961, under the joint auspices of the Indian Pediatric Society and the Association of Indian Pediatricians. Some 250 delegates were present from Asian countries and a few representatives from Australia, Europe, Africa, and the United States. Dr. K. C. Chaudhuri served as president of the Congress. At the opening session many prominent government officials, including President Prasad of India, addressed the Congress. The scientific sessions covered a wide range of pediatric subjects including nutrition, infectious disease, cardiology, child psychiatry, and public health. Most of the communications were in English; simultaneous translation facilities were provided and there was free and lively discussion.

The **Department of Pediatrics of the University of Buffalo School of Medicine** offers a research training program to persons intending a career in pediatric research and teaching. Applicants must have a minimum of one year's pediatric residency; programs will be planned individually for each trainee to include one year in a basic science department of the School of Medicine and one year of research in pediatrics. Stipends are $6,000 first year, $6,500 second year, with $300 additional per dependent up to 3 dependents; funds are available for laboratory expenses and travel. Address inquiries to Dr. Robert Guthrie, Children's Hospital, 219 Bryant Street, Buffalo 22, N. Y.

The **Los Angeles Childrens Hospital** announces a **fellowship** for research in **cystic fibrosis,** involving experimental work, research in pulmonary therapy, and direction of the Cystic Fibrosis Clinic. Applicants are to be Board qualified, preferably with special training in pulmonary physiology; salary will depend on qualifications. Address inquiries to Robert Ward, M.D., Physician-in-Chief, Los Angeles Childrens Hospital, 4614 Sunset Boulevard, Los Angeles 27, Calif.

A 2-year interdisciplinary training program in academic pediatrics is announced by the Department of Pediatrics, University of California at Los Angeles, to include research, teaching, and advanced clinical work, according to the interests and experience of the trainees. Stipends begin at $5,000, with additional allowance for dependents. Applicants must have the M.D. degree or the Ph.D., and in general should have completed at least 2 years' graduate training in clinical pediatrics. Address inquiries to Forrest H. Adams, M.D., Professor of Pediatrics, UCLA School of Medicine, Los Angeles 24, Calif.

The sixtieth meeting of "Der Deutschen Gesellschaft für Kinderheilkunde" (**German Society for Children's Therapeutics**) will take place in Heidelberg, Sept. 11 to 13, 1961.

The **Tenth International Congress of Pediatrics** will be held in Lisbon, Portugal, Sept. 9 to 15, 1962. The scientific program includes three plenary sessions, as follows: I. Problems of the Newborn Infant, II. Pediatric Problems of Tropical Climates and Countries in Development, and III. Pediatric Doctrine. The remaining scientific program is divided into 15 sections

*Notices of meetings must be in the hands of the Editor 3 months in advance of the date in order to appear in the JOURNAL in time.

on specific subjects of topical importance, as follows:

Hematology. (1) Erythrokinetics in the first 3 months of life; (2) acquired hemolytic anemias; (3) hemoglobinopathies; (4) enzymatic disorders of erythrocytes; (5) leukemia (physiopathology and treatment); (6) anemias in the newborn due to fetoplacental transfusion; (7) infantile agranulocytosis; and (8) hemorrhagic diatheses.

Cardiology. (1) Intracardiac phono- and electrocardiography; (2) functional heart murmurs; (3) the evolution of the electrocardiogram in children; (4) the metabolism of the hibernated and arrested heart; (5) myocarditis and myocardosis in infancy; (6) hypertension in childhood; (7) surgical correction of anomalies of venous return; and (8) surgery of septal defects.

Pulmonary diseases. (1) Chemoprophylaxis of tuberculosis; (2) cortisone in the treatment of tuberculosis; (3) infections with *Mycobacterium pseudotuberculosis;* (4) surgical indications in primary tuberculosis; (5) respiratory function; (6) sinobronchitis; (7) fibrosis of the lung; and (8) indications for pulmonary resection.

Neurology and psychiatry. (1) Rehabilitation of children with brain damage; (2) behavior problems of organic origin; (3) psychological sequelae of tuberculous meningitis; (4) thesaurismosis of the central nervous system; (5) parapoliomyelitic diseases; (6) neuroses and psychopathic states; and (7) present problems in education.

Allergy and collagen diseases. (1) Allergic diseases during infancy; (2) infection and allergy; (3) rheumatic fever; (4) collagen diseases; and (5) migraine.

Endocrinology. (1) Influence of endocrine glands upon growth and development; (2) new methods of study of endocrinopathies; (3) endocrine disorders secondary to pituitary insufficiency; and (4) influence of hormones on water and electrolyte metabolism.

Surgery. (1) Postoperative metabolic disorders; (2) diagnosis and treatment of meconial ileus; (3) congenital malformations of the intestine; and (4) surgery of megacolon.

Metabolism and nutrition. (1) Isotopes in metabolic research; (2) anabolic drugs; (3) inborn errors of metabolism; (4) hypoglycemia; (5) malabsorption syndrome; and (6) convulsive and psychopathic states of metabolic origin.

Genetics. (1) New problems in genetics; (2) new methods of study in genetics; (3) genesis of chromosomal aberrations; (4) diseases due to chromosomal abnormalities; and (5) genetics of blood diseases.

Infectious and parasitic diseases. (1) Interference in infectious diseases; (2) the influence of antibiotics in the modification of the natural history of infectious diseases; (3) methods of identification of staphylococci; (4) immunization against poliomyelitis; (5) respiratory viral diseases; (6) adenovirus; (7) enteropathogenic *Escherichia coli;* and (8) echinococcosis.

Pediatric radiology. (1) New methods of radiologic diagnosis; (2) radiologic studies of the central nervous system; and (3) roentgen exploration of the abdomen.

Cancer. (1) Radiation hazards; (2) viral etiology of cancer; (3) cancer in childhood; (4) treatment of sympathoblastoma; (5) differential diagnosis of mediastinal tumors; and (6) tumors of the central nervous system.

Prematurity and postmaturity. (1) Hyaline membrane disease; (2) prevention of prematurity; and (3) the influence of placental function in the length of gestation.

Child health.

Nephrology. (1) Congenital malformations of the urinary tract; (2) renal diseases of the newborn; and (3) acute renal insufficiency.

Submission of papers on the above subjects is invited; an abstract of about 30 typewritten lines for each paper submitted must reach the Secretary General before Nov. 1, 1961.

Applications for scientific exhibits should be made at the time of registration.

A social program is being organized to include sightseeing tours and entertainments; a Ladies' Program is also being arranged. The tourist agency "Tagus" guarantees accommodation in Lisbon hotels to all members; request for accommodation must accompany the Congress registration form.

From Aug. 1, 1961, to Jan. 31, 1962, registration fees for active members are 1,000 escudos (as of March, 1961, about $35.00); for associate members, 600 escudos ($21.00). From Feb. 1 to May 31, 1962, registration fees are 1,250 escudos ($43.75) and 750 escudos ($26.25), respectively. No registrations accepted after May 31, 1962.

The national pediatric associations will have available bulletins of registration for their members. Address other inquiries to the Secretary General, Prof. Dr. Mário Cordeiro, Clinica Pediátrica Universitária, Hospital Santa Maria, Av. 28 de Maio, Lisboa 4, Portugal.

EDITOR'S COLUMN

The overuse of vitamins in children

CURRENTLY the American public is spending some $350,000,000 a year on across-the-counter purchases of vitamins. This sum does not include the cost of vitamins incorporated in foods. It is not possible to estimate what part of this amount is for children but the proportion is probably high.

These expenditures are made in the absence of any evidence showing that healthy children after the first year or two of life, who receive the usual American diet, require additional vitamins or are in any way benefited by them.

VITAMIN SUPPLEMENTS IN SEVERE UNDERNUTRITION

Even children on grossly inadequate diets rarely suffer from demonstrable vitamin lack. A number of observations have been made in children with kwashiorkor. Gomez and his co-workers[1] report cures of this severe nutritional disorder in Mexico by offering a generous diet without the addition of supplementary vitamins. They conclude that seriously undernourished children do not require vitamins other than those present in a balanced diet and those which may be synthesized in their intestines. The observations of Gomez and associates are especially noteworthy since the children they treated were severely ill and many showed symptoms generally considered characteristic of pellagra, ariboflavinosis, hypovitaminosis C, and vitamin A deficiency.

Although differing in some details, the experience with kwashiorkor in Africa has been similar. Hansen, Howe, and Brock[2] state that vitamin supplements are not necessary to initiate cure but that they improve the results. According to the Gillmans[3] the administration of vitamins may have an adverse effect. Kahn* gives vitamins of the B group only if the patient is receiving intravenous fluid therapy and is unable to take milk. Vitamin B_{12} is used when megaloblastic anemia is present.

Keys and others,[4] after an exhaustive review of the literature on human starvation in various parts of the world, conclude that in modern times it is doubtful that vitamin deficiencies are of great importance in the picture of starvation.

VITAMIN SUPPLEMENTS IN HEALTHY CHILDREN

The only vitamin supplements shown to be useful in the routine management of children are D and C and possibly K in the newborn infant. Except under special circumstances, such as the cases of pyridoxine deficiency which were observed in 1951 and 1952,[5] symptoms due to deficiency of the B vitamin group are extremely rare in the United States. During the past 35 years, aside from some children with a rare form of anemia which was benefited by B_{12}, only one child with B deficiency disease, a typical

*Personal communication.

case of pellagra in a 2½-year-old girl, has been observed on the Children's Medical Service at Bellevue Hospital.

Vitamin A deficiency is also extremely rare, being seen with any frequency in the United States only in children in whom fat absorption is interfered with[6] and in children kept for long periods of time on a hypoallergic, milk-free diet without animal fat.[7] The usual diet of children contains ample amounts of vitamin A. On the other hand a number of cases of vitamin A toxicity has been reported. Caffey,[8] writing in 1952, states that 22 cases of chronic A poisoning were recorded in children, all in the United States. He estimates, from his personal correspondence, that many severe cases remain unrecognized.

Vitamin K which is essential for the production of coagulation is widely used to prevent bleeding in the newborn infant. Its introduction for this purpose followed the demonstration of decreased prothrombin activity in the blood of newborn infants and the efficacy of vitamin K in hastening blood clotting. An unfortunate side effect, hyperbilirubinemia, in premature infants following the parenteral administration of large amounts of synthetic vitamin K analogues to mothers has been pointed out by a number of observers.[9]

VITAMIN C

The number of cases of scurvy in the United States has greatly diminished since synthetic vitamin C has become available. The Council on Foods and Nutrition of the American Medical Association[10] recommends a daily intake of 30 mg. per day for infants. This may be given as part of the diet, e.g., 2 ounces of orange juice or as supplements.

The Council recommends further that C supplements be started with the introduction of artificial feeding. The reason for this early administration is not clear, since clinical scurvy is practically unknown before 5 months of age and evidence of "subclinical" C deficiency has not been detected in infants. Park and colleagues[11] found, by special histologic study of the bones at autopsy, changes characteristic of scurvy in 3 infants, newborn, 3 months and 4½ months of age, respectively. In none, however, were clinical manifestations present. According to Vilter,[12] "there is no clear evidence that saturation rather than half-saturation of the body tissues with ascorbic acid will lead to significantly better health, and attempts at supersaturation are not only illogical but wasteful."

VITAMIN D

It is general practice among physicians who care for children to prescribe vitamin C and D supplements for infants during the first year of life.

The great effectiveness of vitamin D in preventing rickets and tetany has been abundantly demonstrated and is ample justification for its widespread use. Rickets and tetany due to inadequate exposure to sunlight or to deficient intake of vitamin D, once an everyday affliction of infants in temperate climates, have been practically eliminated.

Vitamin D is unique among the accessory food substances. For one thing, it has a limited distribution in the natural diet of humans, being present in sizable amounts only in egg yolk and the flesh of certain fishes, notably sardines, herring, tuna, and salmon. Human milk which is otherwise a complete food for normal infants contains almost none, unless the mother is taking food supplemented with vitamin D, in which case small amounts are present.

Second, in the natural course of events vitamin D is a "climatic" rather than a "dietary" agent. It is produced by the action of the ultraviolet rays of the sun which convert 7-dehydrocholesterol in the skin to vitamin D_3.

The antirachitic potency of the sun's rays, which resides in a narrow band in the ultraviolet zone, varies markedly with the season of the year, being greatest during the spring and summer months and lowest during the fall and winter. Even during the winter months, however, sunlight has con-

siderable antirachitic and antitetanic activity. Before the introduction of widespread vitamin D prophylaxis, clinical rickets was unusual in well-cared-for, fair-skinned infants who were taken outdoors regularly during the winter months, even though only the face was exposed. In a study of infants with sunlight-deficiency tetany it was possible to raise the serum calcium as rapidly with artificial ultraviolet radiation as with a daily dose of 11,000 units of vitamin D.[13]

Third, exposure to the sun leads to tanning which reduces the penetration of the antirachitic rays. The antirachitic and tanning rays are close to one another in the ultraviolet spectrum (if not identical) and rise and fall together with the seasons.[14] Presumably, nature promptly provides against excessive D dosage through irradiation by raising a barrier in the skin.

The Council on Foods and Nutrition of the American Medical Association recommends a daily intake of 400 U.S.P. units of vitamin D for infants.[10] This is the amount customarily used in the United States to supplement a 13-ounce (390 c.c.) can of evaporated milk and a quart (960 c.c.) of whole milk. Artificially fed babies receiving these amounts of milk daily, therefore, require no added vitamin D. During the early weeks of life when the growth rate is rapid and the milk intake less than a quart, additional vitamin D may be advisable.

The Council states further that retentions of calcium and phosphorus are maximal with 300 to 400 U.S.P. units of vitamin D and that excessive amounts—1,800 U.S.P. units or more daily—decrease appetite, reduce retentions of calcium and phosphorus, and slow linear growth.[10]

The requirement for vitamin D depends on the age, which in turn is closely correlated with the growth rate; on the season of the year and the amount of exposure to sunlight; on the skin color, skin pigmentation being a potent barrier to the action of the ultraviolet rays; and on the calcium intake. Absorption of vitamin D through the intestinal tract is greatly reduced in diseases in which fat absorption is impaired, e.g., celiac disease, liver disease, and larger dietary supplements, therefore, are necessary.

The requirement for vitamin D is greatest during the first year of life when the growth rate is more rapid than at any time during postnatal existence. It is necessary throughout life. Osteomalacia due to sunlight or vitamin D deficiency has been described in Chinese women who remain indoors during pregnancy according to ancient custom and who, at the same time, receive an inadequate diet.[15] Tetany was not infrequent during the nineteenth century in men who worked in factories or shops where they were not exposed to sunlight. Patients suffering from vitamin D–resistant rickets, even in adult life, relapse unless supplements of vitamin D are provided.

The amount of vitamin produced by the action of sunlight on the skin is apparently adequate for normal adults. During the spring and summer months when sunlight is ample and babies are exposed freely, no supplementation is necessary, and the use of vitamin D–reinforced milk is superfluous.

Skin color is an important consideration in prescribing vitamin D. Before the widespread use of D prophylaxis, rickets was well-nigh universal in Negro babies in temperate climates during the winter and spring months. It seems wise, until contrary evidence is presented, to prescribe D supplements to dark-skinned infants in addition to the D in reinforced milk.

The Council on Foods and Nutrition of the American Medical Association recommends a daily intake of 400 units of vitamin D throughout the growth period. Presumably, the recommendation for continuing D supplements after infancy is based on two sets of observations. In 1943 Follis and his colleagues,[16] on the basis of autopsy studies, reported that almost 50 per cent of children between the ages of 2 and 14 years showed rachitic changes in the bones. The prevalence was no greater in Negro than in white children, but the more severe changes were found among the Negro children. Roentgenologic evidence of rickets was not found

after 4 years. Some of the children had received vitamin D supplements.

The second piece of evidence for continuing vitamin D throughout the growth period is the observation of Johnston[17] that an increase in calcium retention is favored by vitamin D administration in adolescents.

The clinical significance of the morphologic studies of Follis and co-workers and the metabolic observations of Johnston is not clear. Before the general use of vitamin D prophylaxis, rickets and tetany were extremely common in infants but they were almost never seen after the first 2 or 3 years of life, even in dark-skinned children. The various authors make no claim for any clinical advantage to administration of vitamin D.

It is doubtful whether increased calcium retention is beneficial. Calcium, unlike phosphorus, has a limited distribution in the diet, being present in sizable amounts only in milk and milk products, notably the cheeses. In the animal world in general the ingestion of milk is limited to the nursing period. The calcium content of human milk is low, being only 25 per cent that of cow's milk.

Adverse effects. Shortly after concentrates of vitamin D were introduced for the prevention and cure of rickets, Alfred Hess[18] cautioned against the dangers of overdosage. He considered it unwise to add this "drug" indiscriminately to milk for infants.

The adverse effect of large doses of vitamin D on linear growth, appetite, and calcium-phosphorus retention during the first year of life has already been mentioned. Growth with daily doses of 1,800 units of D or more is about the same as that of infants receiving only 135 units and is definitely slower than the growth of infants receiving 340 units.[19]

At the annual meeting of the British Paediatric Association in 1953 Lightwood and Payne[20] described 10 infants with hypercalcemia who presented a homogeneous clinical picture. The babies did well until they were 3 to 7 months of age when anorexia, vomiting, wasting, and constipation appeared. Some were dehydrated, and in about half thirst, polyuria, and spikes of fever were also present. Blood changes were, in addition to the hypercalcemia, an elevation of the blood urea and the plasma proteins. The condition persisted for 5 to 15 months after which slow spontaneous recovery took place.

A severe type of infantile hypercalcemia with physical and mental retardation, patchy osteosclerosis, renal failure, and hypertension has also been described.[21] Early death is not infrequent. In this small group of cases the metabolic error is, apparently, an endogenous formation of excessive amounts of vitamin D.

Following the report of Lightwood and Payne a large number of cases of hypercalcemia in infants were recognized in Britain. A survey showed that 196 pediatric consultants had seen 204 such patients between 1953 and 1955. In Dundee, a city of 450,000 inhabitants, 4.6 per cent of all medical hospital admissions of infants, 6 to 12 months of age, were due to infantile hypercalcemia, and it had become the fourth most frequent reason for admission.[22] Cases have been seen in Finland, Norway, Portugal, Sweden, Switzerland, and the United States.[23]

Most students of the syndrome believe that the probable cause is overdosage with vitamin D. Stapleton, MacDonald, and Lightwood[24] calculated that infants in Britain who were taking 1½ pints of reconstituted dry milk (1,725 I.U.), one ounce of fortified cereal (1,500 I.U.), and a teaspoonful of fortified cod liver oil (700 to 800 I.U.) distributed without cost in welfare stations could be getting as much as 4,000 I.U. of vitamin D per day. Elevated levels of the vitamin in the serum of a child with idiopathic hypercalcemia have been recorded.[25]

The virtual disappearance of infantile hypercalcemia in Britain following the reduction in the amount of vitamin D incorporated in milk and the lessened use of supplements subsequent to the wide publicity given to the subject of D intoxication is generally considered strong confirmatory

evidence that D is, in most instances, the offending agent in infantile hypercalcemia.

A striking feature of vitamin D intoxication is the relatively narrow margin between the physiologic and toxic doses. Whereas with vitamin A the prolonged use of about 40 to 50 times the usual amount is necessary to produce toxic symptoms, in the case of D only 4 to 5 times the ordinary amount induces adverse effects.

WHO IS AT FAULT?

It is customary to place blame for the widespread, indiscriminate use of vitamins in children on the drug companies and their aggressive sales tactics. Undoubtedly vitamins have been pushed with a zeal which is hardly justified by their health value. But pediatricians have acquiesced in this program when they have not actively supported it. Certainly they have not actively opposed it.

In order to gauge the attitudes of leading American pediatricians on the vitamin needs in children a simple questionnaire was circularized among directors of pediatric teaching services. The questions asked were:

1. Do you believe that most of the children on your service should have supplementary vitamins?

2. Do you know what vitamin preparations are used on your service? Do you know what they contain?

3. Who decides what vitamin preparations are used on your service?

Replies were received from 26 out of 27 who were surveyed. In almost every instance amplifying statements were appended. Undoubtedly the leaders of American pediatrics are concerned about the overuse of vitamins in children and appreciate its importance.

There was general agreement among those surveyed that vitamins D and C should be given during infancy. Some also added vitamin A, presumably because all natural foods which contain vitamin D also contain vitamin A. Only 5 of the 26 professors of pediatrics stated that vitamin supplements should be given to children after infancy. A fourth said that "D might be continued after infancy but there is little clinical evidence that it is needed." Another said, "vitamins D and C should be given up to 3 to 5 years of age, particularly in hospital practice. Not for private patients." In general the professors deplored the widespread prescribing of vitamins by their staffs but felt that they were unable to control it.

Most of the men declared that they knew what preparations were used on their services and what they contained. The choice of a preparation was usually made by the pharmacy committee, but in many instances the house officers made the decision, often on the basis of the availability of free samples. The director of a large university service described his experience in the following words, "I found that, in spite of numerous admonitions to the house staff about unnecessary vitamins, they were prescribing multivitamin preparations and were faced with the problem that it was virtually impossible to obtain anything else. I tried to get the hospital to buy a preparation containing A, C, and D, but, before this was approved, competing firms offered to sell multivitamin preparations at a lower price. I finally succeeded in getting a preparation containing A, D, and C on the wards, but I haven't checked lately to see what is actually being prescribed. I suspect that the house staff is being waylaid on the way to the dining room and may have been persuaded to go back to multivitamins."

The purchase of vitamins generally goes to the lowest bidder provided minimum requirements are met. In the last analysis the hospital purchasing agent usually decides which vitamins the children will receive.

The replies brought out that, with a few exceptions, the leaders of American pediatrics do not regard the routine use of vitamin supplements as useful after infancy, even in the case of vitamin D which is recommended by the Council on Foods and Nutrition of the American Medical Association. But, despite their convictions, they do not seem to feel that the subject is of sufficient importance to be brought before their staffs forcibly. Conferences are devoted

to discussions of abstruse metabolic problems which are new and fresh and which delight the imagination, but this everyday, pedestrian subject is bypassed. Consequently house officers leave their hospitals with the idea that, as long as children get vitamins, it does not matter very much which ones, how much (the more the better), or until what age. No concerted effort is made to immunize the young physician against the blandishments of the "detail man," the free samples, and the repetitious advertisements. It is, therefore, not surprising that vitamins are prescribed indiscriminately, even by graduates of the best training centers.

As an example of the apathy of the profession, the principal American pediatric journals publish advertisements for products which contain 1,000 units of D per dose. (Some ads do not state the vitamin content). This amount of D, when added to the 400 units in milk and the D incorporated in foods, provides an intake closely approximating the 1,800 units shown by Jeans and Stearns[19] to affect growth adversely.

The pediatric journals also carry advertisements which advocate the use of vitamin B_{12} to increase appetite. There is no good evidence for this claim. The Committee on Nutrition of the American Academy of Pediatrics, after surveying the literature, concluded that "claims for any effect of these vitamins (B_1 and B_{12}) in either stimulating appetite or promoting growth are not justified."[26]

Aside from a strongly worded editorial by May[27] the recent American pediatric literature contains no criticism of the overuse of vitamins in children. Currently the American Medical Association has begun a campaign along these lines.

WHAT SHOULD BE DONE?

The public has become so firmly indoctrinated with the false idea that vitamins are valuable health aids that a major effort will be required to alter the situation.

A first step in combating the misuse of vitamins is the education of physicians in their proper use. The physician, from the very inception of his career, should be given a solid training in this everyday subject, and the facts should be discussed again and again on ward rounds and at teaching sessions. At present students and house officers receive their principal indoctrination about vitamins from the detail men who can hardly be expected to present an objective estimate of their products.

How poorly grounded the young physician is about the subject of vitamins is illustrated by the replies to a question which was recently posed by the American Board of Pediatrics.[28] The question, requiring the answer "true" or "false," was:

It is essential for health that a child's diet furnish adequate vitamin C every day *because* present evidence indicates that his body is unable to store vitamin C.

Both the statement and the reason are false, but only 4 per cent of the 520 American candidates answered the question correctly; and even among the top candidates a mere 7 per cent recognized that both statement and reason were false.

The Board attributed the failure to answer the question correctly to indoctrination by repetitious advertising. But, it seems to me, the fault lies primarily in our failure to indoctrinate students and house staff thoroughly in the facts about vitamins and thereby immunize them against false claims.

Physicians should appreciate that the indiscriminate use of vitamins is superfluous, wasteful, and at times harmful. In children, where the placebo effect is rarely a consideration, the indications for prescribing vitamins should be as clear-cut as for any potent drug. Only those preparations should be prescribed which contain the required vitamins in proper amounts.

Education of the laity is essential. An excellent beginning has been made by the American Medical Association and by *Consumer Reports* in its September, 1960, and January, 1961, issues. *Today's Health,* a journal for the laity published by the American Medical Association, is no longer accepting advertisements for vitamins and vitamin-mineral preparations. The American

Academy of Pediatrics has now extended its activities to health education, and it is hoped that appropriate literature informing the public about the proper use of vitamins in children will be available for distribution among parents.

Finally, editorial boards of pediatric journals should carefully scrutinize advertising copy which is submitted, and advertisements which make false or extravagant claims should be rejected.

SUMMARY

1. About one million dollars a day is spent on vitamins in the United States, much of it for children.

2. The consensus of the large majority of leaders of American pediatrics is that vitamin supplements have no value for children after infancy, except where there are specific indications.

3. The danger of vitamin D overdosage is emphasized.

4. The training of physicians in regard to the appropriate use of vitamins should be intensified, especially in medical schools and in residency programs.

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Pediatrics and nuclear medicine

THE pediatrician has long been familiar with the value of x-rays in the investigation and diagnosis of childhood illness and to a lesser extent with their application in therapy in conditions such as intussusception and neoplasia. He is also becoming increasingly aware of the harm which may result from the excessive use of diagnostic radiation. In recent years, radioactive isotopes have become generally available. Although they have proved extremely useful in research, their precise role in pediatric diagnosis and treatment has been less clearly understood. The knowledge that their use in children may be associated with both real and unpredictable hazards has led to hesitation and confusion on the part of the pediatrician. On the one hand he is tempted to make use of a new tool which may lead to earlier diagnosis, shorten hospitalization, and point the way to clear-cut approaches to therapy. On the other hand he is restrained by concern about the possible late effects which may follow exposure of a young growing organism to radiation.

The infant and child present special problems in radiation medicine because they are growing organisms and because their life expectancy provides extra opportunity for cumulative exposure over a long period of time, not only to diagnostic x-rays but also to outside sources of radiation such as cosmic rays and radioactive atmospheric debris. The possible long-term genetic effects have also to be considered.

An opportunity to observe and discuss the present status and future implications of nuclear medicine with experts in the field was presented to some 75 chairmen of pediatric departments of American and Canadian medical schools late in March when they were invited to visit the Brookhaven National Laboratory as guests of the Division of Biology and Medicine of the Atomic Energy Commission and the Medical Department of the Brookhaven National Laboratory. Research and education in the area of nuclear medicine are the prime objectives of the Medical Department of the Brookhaven National Laboratory. Yearly conclaves have been organized in order to make sure that those concerned with medical education are made fully aware of the extraordinary facilities available at this center for investi-

gation, research, and the education and training of young scientists. This was the fifth such conference since 1956. Previous meetings have included chairmen of departments of pathology and surgery and the deans of American and Canadian medical schools. That the radiobiological experts at Brookhaven consider pediatrics an important area for education and research in nuclear medicine may be inferred from this early involvement in the conference program.

The Brookhaven program makes available in one area expensive and highly specialized equipment and a staff of both medical and nonmedical scientists dedicated to the extension of knowledge in the multidisciplined area of nuclear science. The plant is operated by the Atomic Energy Commission as an integral part of its nationwide program in conjunction with a cooperative group of nine northeastern universities. The provision of those facilities which could hardly be provided by any one university makes possible the active pursuit of research in radiobiology by a group of full-time senior scientists and visiting scientists as well as the training of young university graduates.

The two-day session consisted of three introductory lectures followed by a series of some twelve demonstrations to small groups of the special equipment facilities including the medical research reactor, the 60-inch cyclotron, the new alternating-gradient synchrotron, as well as various radioactivity counting devices including the new whole-body counter. Research projects with special application to pediatrics were demonstrated and discussed in group conference by members of the research staff. Of special interest was the demonstration of the production of lesions in the "satiety" center of the ventromedial hypothalamus with the use of gold thioglucose subjected to neutron activation. By means of radioautography it was shown that the gold and probably the sulfur moieties of gold thioglucose accumulated in well-defined areas of the ventromedial hypothalamus in all animals that developed increased appetite and obesity but not in control animals. The application of neutron capture therapy employing boron in the treatment of deep-seated neoplasms was demonstrated. There was remarkable regression of tumor tissue in a malignant cerebellar neoplasm in a child treated by this technique. Clinical improvement occurred and lasted several weeks. Relapse and death then followed. At autopsy a small deep-seated nubbin of tumor remained, a small fraction of the size of the original tumor. Microscopic section showed complete disappearance of tumor cells except in the small unresolved area. The surrounding brain tissue was histologically normal.

During the ensuing discussion on the hazards of radiation, some of the risks involved in diagnostic radiology were stressed and are worth noting here. The special dangers associated with conventional fluoroscopy were mentioned. It came as a shock to some of us to learn that a one-minute exposure of a child to fluoroscopy was equal in radiation dosage to 300 chest films. The recommendation made by Caffey[1] last year and repeated at this conference that image intensifiers be made available for fluoroscopy in all children's hospitals as soon as possible seems not only reasonable but a matter of real necessity in the light of present knowledge.

Perhaps the most important point made was that radioactive isotopes should *not* be used in the childhood age groups unless and until all other diagnostic or investigative avenues had been exhausted. Even then, there must be a positive indication for their use. As has been stated recently,[2] "No real physical harm has ever been done by performing too many blood counts on a given patient, but this may not be true with children who are subjected to repeated I^{131} uptakes to determine thyroid function, radioactive isotope dilution measurements of blood volume, edema or other body composition deviations or to other procedures involving the use of radioactive isotopes." In other words, for the time being radioactive isotopes should be used only to obtain essential information not otherwise obtainable or when they may contribute quickly

to a definitive diagnosis where time is of the essence if lifesaving measures are to be instituted.

It is obvious that the pediatricians of today and the undergraduate medical students, some of whom will be the pediatricians of tomorrow, must become familiar with the principles and objectives of nuclear medicine. As stated by Farr,[3] "It is not expected that each pediatrician will become an expert in nuclear medicine, but it is obligatory that he become thoroughly familiar with its objectives and principles, just as he is with those of surgery or psychiatry, in order that he may exercise proper judgment with respect to referring his patients to an expert in the particular procedure of nuclear medicine." The teaching of the principles of radiobiology should of course be included in the undergraduate medical curriculum. The inclusion of the teaching of nuclear medicine as it relates to pediatrics in the already overcrowded resident training program constitutes a real problem. Some experience may of course be gained by observing the methods used by members of the teaching and research staff. Radioisotope committees in each medical school, headed by faculty members with special training but including a representative of the pediatric department, could assume the responsibility for teaching residents the principles and objectives of nuclear medicine as applied to pediatrics.

For the pediatric resident preparing for a career in teaching and research a much more thorough training in nuclear medicine is necessary. Whatever reservations may be made about its application to the actual care of infants and children, there is little doubt about its tremendous value in research. Association with an expert in this field for a reasonable period or, better still, a period of training at Brookhaven as a preliminary step in such a career would be most desirable.

The pediatric conclave at Brookhaven was an informative and stimulating experience for all who attended. To Lee Farr, Lewis Dahl, and their associates who performed so well as "educational donors" our thanks for the opportunity to serve as "educational recipients" in an exciting area of pediatric interest.

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The control of poliomyelitis

METHODS of achieving protection against paralytic poliomyelitis have occupied scientists for the half century since the discovery of poliovirus. The first major clinical effort to do so occurred in the United States in the mid-1930's with vaccines made of formalinized or ricinoleated virus-infected monkey spinal cords. The results were not at all encouraging if not actually disastrous.

Only in the past decade has a firm biologic foundation been laid upon which to build plans and hopes for safe effective polioimmunization. The brilliance of the progress made in this short time plus the glare of public interest have blinded some who prematurely concluded that little remained to be done in polio prevention and research. A decade is too short a time to expect this.

The recent scientific foundation of current progress in this field rests upon the following five points: (1) There are but 3 serotypes of poliovirus. (2) Tissue cultures of large amounts of poliovirus can now be made. (3) Polio antibody when present in blood serum prevents viremia and paralytic manifestations. (4) Suitable formalin treatment of poliovirus destroys infectivity with retention of its immunogenic properties. (5) Laboratory manipulation has converted certain strains of wild poliovirus into the attenuated state free of paralytogenic properties and useful for feeding as a vaccine.

It should be emphasized that these 5 facts represent the *scientific* foundation for polio prevention. That social, cultural, and psychological considerations are also vital should be apparent, and may be dramatically exemplified by tetanus, which continues to occur and to kill despite the existence of a simple, superb, purified, inexpensive vaccine readily available much longer than the rather new poliovaccines.

Any consideration of the prevention of poliomyelitis should take into account time, place, and circumstance. Here attention is largely centered on countries of the Western Hemisphere, but there is recognition of numerous significant variations even within the same country. Since poliovirus is no respecter of national borders, eradication of disease would ideally be achieved by eradication or supplanting of dangerous strains of wild poliovirus. This goal is precisely the hope of proponents of mass immunization with attenuated poliovaccine given by mouth.

Today's difficulties with poliovaccines are both scientific and otherwise. The press has left with many the impression that one has only to choose between Salk vaccine and the Sabin oral vaccine as between two beverages or two automobiles. Each form has an important place at present; individual circumstances of time and place may determine which one at a given time is most applicable. In overpopulated, underprivileged areas, oral vaccination has numerous advantages.

The different principles of the two approaches to immunization deserve comment. Natural immunity is achieved through alimentary infection resulting in serum antibody as well as in local resistance or immunity of the gut; thus a previously infected person resists alimentary reinfection and is not only himself protected, but ceases to be a potential shedder of virus. These are also the principal effects of Sabin's vaccine strains. Intramuscular vaccination with Salk-type formalinized vaccine given to persons who have never had natural infection with the three serotypes of poliovirus gradually results in protective serum antibody but not in local resistance of the gut. In the gut of such individuals poliovirus can multiply and be shed as before.

The chief advantage of Salk vaccine is its established effectiveness in recipients who have received sufficient quantities of antigenically potent material. The significant disadvantages include: (1) the further need to purify and concentrate the contained antigens (Hilleman's method for Purivax is a step in this direction); (2) uncertainty about the frequency and number of booster doses needed as evidenced by the occasional occurrence of paralytic poliomyelitis in spite of 4 or more injections; (3) the fact, according to the Surgeon General of the Public Health Service, that 85 million persons in the United States alone have not been adequately Salk immunized. This low acceptance rate is distressing.

The advantages of feeding attenuated polioviruses include the painless simplicity and effectiveness for the patient, and the development of intestinal resistance to wild strains of poliovirus. The significant disadvantages include: (1) a nagging fear, for which there is no evidence with Sabin strains, that attenuated viruses will revert to the wild paralytogenic state, and (2) that, initially, at least, mass simultaneous feeding is desirable which may bring on certain medical administrative problems.

Both kinds of vaccine are prepared from monkey kidney tissue; elaborate precautions in the procurement and handling of monkeys and testing for extraneous infectious agents

are necessary. A number of new simian viruses have been identified whose disease potential for man remains obscure. The use of formalin in Salk vaccine has been regarded as a safety factor not present in attenuated live vaccines, but even this may not stand the test of time. Thus last year when Sweet and Hilleman[1] described yet a new simian virus (vacuolating agent), a further dilemma and obstacle arose in the preparation of live poliovaccine. Now comes a report from Great Britain[2] indicating that vacuolating agent is resistant to formaldehyde and that its inactivation kinetics are such that "the virus would be present at the end of the routine Salk process if the initial virus titer is in the range of 10^6, a fairly common finding in Rhesus-monkey-kidney cultures." These authors go on to make the point that such virus when swallowed does not appear to propagate or to penetrate the tissues, and this writer agrees.

It is likely that many of the more than 100 million individuals fed attenuated poliovaccine in Europe and elsewhere swallowed vacuolating virus and other as yet undiscovered latent viruses. Only time will tell whether adventitious "nonhuman" viruses have hidden harm by this route of administration. On general biologic grounds one would predict that the human alimentary tract is better able to dispose satisfactorily of much foreign stuff encountered in nature and/or manufactured by man than could the body deal with injected agents. This is no excuse to postpone attempts at purification, but rather a considered judgment in taking certain potential risks always present in medical practice.

Most readers are familiar with the schedule for Salk poliovaccine proposed by the Academy of Pediatrics which consists of four doses of vaccine followed by biennial boosters. For oral vaccination with attenuated strains of virus the following gives some idea of what current authoritative opinion is considering: monovalent type 1 virus by mouth to all newborn infants within 3 days of birth, to be repeated in 6 to 8 weeks; then monovalent type 3 virus at 3 months of age; monovalent type 2 at about 4½ months of age and the trivalent mixture of types 1, 2, 3 at 10 to 12 months of age. For the general population the thought is to vaccinate during the polio "off-season" (November to June), feeding virus types 1, 3, and 2 in that order at 6-week intervals. For this portion of the program it is considered very important to have as many people fed simultaneously as possible. Simple syrup or candy may be used as the vehicle.

This kind of schedule for oral vaccination is neither official nor final, but is quite different from the impression the general public may have that a single trivalent dose taken once is all that is needed for a lifetime. To make such a program effective requires the fullest measure of physician cooperation and patient acceptance. Unless live virus vaccine is accepted more universally than Salk vaccine has been its value will be limited.

The four recognized goals in poliomyelitis control are: (1) prevention of epidemics; (2) curtailment of epidemics once under way; (3) prevention of endemic poliomyelitis, and finally (4) eradication of paralytic strains of poliovirus.

To achieve all of these goals this writer shares the opinion of those who believe that the oral administration of attenuated strains of poliovirus will be necessary. Until such time as production and programing for its use overcome the many obstacles placed in the path of the widespread use of oral vaccine, maximum use of Salk vaccine must be intensified, especially among infants, parents, and people of all ages in the lower socioeconomic groups. Propaganda is desperately needed to ensure wider use of both kinds of immunizing agents as they now exist, and more intensive research to improve both types must not be slackened. A Salk-type vaccine free of extraneous proteins, antibiotics, and adventitious viruses, concentrated and attached to an acceptable adjuvant might with perhaps 3 injections and no booster doses achieve what cannot now be assured with a much longer series. The production of either Salk-type or Sabin live vaccines from tissues less likely than kidney

tissue to harbor latent viruses would be an important forward step. A highly vascular organ of excretion, the kidney may be expected to shed and harbor many viruses. In recent years the number of viruses recoverable from human urine is zooming and some may lurk undetectable in the kidney for long periods of time.

There is now and there will be for some time an important role for both formalinized and oral types of poliovaccine. Full steam ahead now with both of them, combined with continued laboratory research, together with social research into the human factors (including physicians' reactions as well as those of the public) of acceptance and utilization of these vaccines should be the order of the day.

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REFERENCES

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